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AN INTRODUCTION TO THE STUDY OF THE ENDOCRINE GLANDS AND INTERNAL SECRETIONS

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LECTURE I.

General Considerations Regarding Internal Secretions and the Organs Which Furnish Them.

Material which is passed into the blood or lymph from any tissue or cell of the body forms what has been termed its *internal secretion,* and organs which are not known to possess any other function than that of passing such material into the blood or lymph are termed *internally secreting* or *endocrine organs.** But this term is not usually extended to organs like the lymphatic glands of which the material production is of a morphological character, although until recently all such organs used to be included along with the true endocrine glands, the functions of which were at that time unknown, in the general expression of *ductless glands.* Under this last term were comprised not only the thyroid (to which must be added the parathyroids), the suprarenal capsules or adrenals, the pituitary body or hypophysis cerebri, and the pineal gland or epiphysis cerebri, to which we now commonly ascribe internally secreting functions, but also the thymus gland, the tonsils, lymph-glands and lymph-follicles, and the spleen; with these the bone-marrow must also be associated. Regarding the thymus gland, although some evidence has been adduced that it may yield an internal secretion to the blood which exercises a specific action upon the functions of growth and development, especially of the generative organs, it appears both developmentally and structurally to present undoubted resemblance to the tonsils, which are universally allowed to be structures of a lymphatic nature, and most of its cells are lymphocytic in character. Some have supposed that the spleen also provides an internal secretion which is destined to affect the quantity of the pancreatic juice. But the proof of the existence of such internally secreting functions in connexion with these lymphoid organs is so inferior to that which we possess regarding the thyroid, parathyroids, adrenals and pituitary, and even the

*From ἔνδον, within, and κρίνω, to separate.

pineal gland, that we may, at least provisionally, exclude them from the class of organs which are known to secrete active chemical agents into that fluid for the purpose of influencing other organs. It is to this latter class that I intend to restrict my remarks, and it is to them and them alone that the term ''endocrine organ'' will be applied in these lectures.

It follows from what has just been said that by the expression ''endocrine gland'' we imply an organ which is known to form some specific chemical substance within its cells and to pass this directly or indirectly into the blood stream. The substance thus formed is the active material of its secretion, just as ptyalin is the active agent of the salivary secretion. But while in the case of the salivary glands the secretion is conducted by a duct to the exterior, in the case of the ductless glands the secreted material remains within the body and circulates with the blood; hence the term ''internal secretion'' commonly applied to it.

The expression "internal secretion" was originally applied in a sense somewhat different from that in which it is now used, having been first employed by Claude Bernard to describe the grape sugar which, as he showed, is passed from the liver cells into the blood. It has also similarly been used to designate all materials which are contributed to the blood by the tissues. In this manner the carbon dioxide and other products of metabolism which are taken up by the blood in its passage through the capillaries or are received by it through the medium of the lymph stream would be internal secretions and every tissue would be an internally secreting structure. It is, however, convenient to restrict the term "endocrine" to substances of a specific nature like the active chemical agents which are produced by the ductless glands, and this is the sense in which the expression will be employed in these lectures.

But it is proved that the production of specific chemical agents which are passed into the blood and carried by it to distant structures is not confined to the ductless glands—that an active internal secretion may be produced by other organs than these. A notable example is met with in the case of the pancreas, the obvious and long known function of which is the production and excretion into the intestine of pancreatic juice; which, by virtue of the ferments it contains, is the most active agent in the digestion of food stuffs within the alimentary canal. In 1889, however, it was shown by v. Mering and Minkowski that the pancreas possesses an internal secretory function which is of even greater importance in the economy than its long recognized external secretory activity. For by totally removing the pancreas in animals these observers proved that the presence of the gland and of some material yielded by this gland to the blood is essential to the proper utilisation of carbohydrate material in the tissues, so that if the organ be removed

grape sugar is no longer stored in the liver, and little by little split up by the organism into simple oxidisable substances, but is passed out from the blood in which it is in excess by the kidneys, thus producing glycosuria. It may be added that our present knowledge of the etiology of diabetes is mainly based on these observations.

Now it is known that the pancreas possesses, besides the secreting alveoli which form the enlarged and blind terminations of its ducts, a special kind of secreting cells which are massed together into islets of irregular shape and variable number and size, having a special kind of blood supply. These islets, which were first described as a distinct element of pancreatic tissue by Langerhans, have been originally developed from and may retain a connexion with the ducts of the organ, in this respect resembling the ordinary alveoli. But in the course of growth they have lost all open connexion with the ducts; their cells have acquired specific properties; and their function is without doubt different from the ordinary cells of the gland. With some show of reason the special internal secreting function which has been above mentioned has been ascribed to them, and in support of this it may be stated that in many if not most cases of diabetes these cells are found to have undergone degeneration. They in fact form an organ within an organ, and may be collectively regarded as belonging to the group of internally secreting or endocrine organs.

An example of a tissue which is devoted to the formation of both an external and an internal secretion is found in the epithelium which lines the duodenum. The functions of this epithelium which have been longest known are those of aiding in the absorption of digested food materials and of helping to furnish the material known as the intestinal juice. But in 1902 it was discovered by Bayliss and Starling that if an extract of the duodenal epithelium is boiled with dilute hydrochloric acid and after neutralization is injected into the blood stream of an animal a rapid flow of pancreatic juice is determined. It had already been known that the gush of acid gastric juice through the pylorus or the painting of the mucous membrane of the duodenum with dilute acid would determine a flow of pancreatic juice, but this flow had been supposed to be brought about as a reflex act by excitation of a local nervous mechanism by the acid. The observations of Bayliss and Starling rendered it clear, however, that this is not the correct explanation of the phenomenon; but that the flow must rather be regarded as due to the absorption of some internal secretion into the blood: the material of this internal secretion being produced in an inactive form by the epithelium cells and becoming so altered by the dilute acid as to be converted into an agent which, after

absorption into the blood stream, excites the secreting cells of the pancreas to activity.

To the active substance which is yielded by the epithelium cells of the duodenal mucosa the name *secretine* was given by Bayliss and Starling, whilst they termed *pro-secretine* the inactive material contained within the cells before the action of dilute acid upon them. The active material is obviously of the nature of an internal secretion; it appears, however, not to be produced by a special structure, certainly not by a special organ; but so far as one can tell, by the ordinary cells which line the mucosa and extend into its glands.

A similar but not identical internal secretion has been shown by Edkins to be produced by the cells of the mucous membrane of the pyloric end of the stomach. When rendered active and absorbed into the blood this secretion, which is termed *gastrine* by Edkins, stimulates not the cells of the pancreas but those of the fundic glands of the stomach itself.

A yet more remarkable example of the coincidence of external and internal secretory functions in the same organ is supplied by the generative glands (ovary and testicle). It has been known from time immemorial—the experiment is repeated daily for commercial purposes in thousands of animals, and is still practiced upon man for domestic reasons in certain Oriental countries—that the removal of the generative glands in the young male animal usually entirely prevents the development of the accessory generative organs, such as the prostate, and of the features which characterize the male sex externally. These changes may be prevented by successfully grafting a testicle in the castrated animal.

Again, removal of the ovaries in the young female exerts a profound influence over the organism and prevents the development of many female characteristics. In some cases, even in the adult, removal or atrophy of the ovaries has been noticed to lead to the development of male characters. Instances of this have been often recorded in birds. In young mammals removal of the ovaries is followed by arrest of development of the uterus. This may be prevented by successfully transplanting the ovaries or by grafting an ovary from another animal of the same species into the peritoneum or elsewhere. It seems clear, therefore, that the result of removal is due in both male and female to the absence of the internal secretion of the generative gland.

The Nature and Mode of Action of the Active Principles of the Internal Secretions.

We have compared the active materials of the internal secretions, which are formed within cells and passed out into the blood, to the active

agents of the ordinary secretions, which are directed on the exterior by means of a duct. But the comparison cannot be pressed. In the case of the external secretions, the active agents when present are always of the nature of a ferment. They belong to the class of bodies which are known as *enzymes.* The conditions and modes of action of these bodies are for the most part familiar to the biologist. They occur not only in secretions but in the bioplasm of most if not of all cells; indeed the chemical activity of the cell in most if not in all cases depends upon its contained enzymes. Although far simpler in chemical nature than the bioplasm by which they are produced, and in no sense endowed with life, enzymes are very probably of a protein nature, and they are readily destroyed by heat in presence of water. The active materials of the internal secretions, on the other hand, are for the most part not rendered inactive even by prolonged boiling, and are certainly of a much simpler chemical constitution than enzymes. They are dialyzable; and although most of them have not yet been isolated in a crystalline form, due probably to the fact that it is difficult to obtain them free from impurities, some of them have been so obtained, and at least one—the active material of the adrenal medulla—has been prepared synthetically. They for the most part act readily upon the cells which they influence—at least this is the case with those which can be extracted by water from the organs which produce them—and the extracts often exert an immediate effect when injected into the blood; whereas it is usually the nature of an enzyme to operate more gradually. The action of the principles contained in the internal secretions and capable of extraction by watery fluids is in point of fact not very dissimilar from that produced by the active principles of drugs, especially those of organic, i. e., of vegetable origin. These also operate by immediate chemical action, being conveyed to the parts which they influence in solution in the circulating blood. As with drugs, some of the principles contained in such extracts of the endocrine organs act by stimulating or exciting cell-functions: this is notably the case with the principle obtained by the action of acid on the duodenal epithelium. Others depress or inhibit those functions: an example of this is met with in extract of placenta, which when injected into the bloodvessels tends to inhibit the secretion of milk. To such stimulating principles, as that contained in the extract of duodenum after treatment with acids, the term *hormone* (from ὁρμάω, to stir up) was originally applied by Starling,* and the expression has been extended to include the active principles of all internal secretions. As long as only exciting agents were known there

*Verhandl. 1.

could be no objection to this extension of the term, but since agents which produce depression or cessation of function have been shown also to be produced in the endocrine glands—and their number will probably become considerable as the nature of the internal secretions is more fully examined—it is advisable to employ an expression which will discriminate between these and stimulating agents. I propose therefore to distinguish the action of the depressants from that of the excitants by the use of the term *chalone* (from χαλάω, to make slack). A *chalone* may therefore be defined as an endocrine product which inhibits or prevents the activity of an organ or tissue, as distinguished from a *hormone,* which excites the tissue to increased activity.*

Starling does not, however, confine the use of the term "hormone" to organic principles of an endocrine nature. His definition is much wider. "By the term 'hormone,' " he says, "I understand any substance normally produced in the cells of some part of the body and carried by the blood stream to distant parts, which it affects for the good of the organism as a whole." (*Proc. Roy. Soc. Med., Vol. vii., Therap. and Pharm. Sect., p.* 29). He then proceeds to give as examples of hormones, secretine, adrenine, and carbonic acid—the last, which is produced by the tissues in general and more especially by muscular tissue, stimulating the respiratory centre to activity. Obviously this definition would include most substances normally present in the blood, such as water, urea, glucose and inorganic salts, which are produced in various parts of the body and affect distant organs such as the kidneys: indeed it may be supposed that all substances in the blood will, when we know more about their history, come into the definition. The expression *hormone* has not been hitherto employed by physiologists and clinicians in this extended sense; the term has invariably been restricted to the active organic principles of the internal secretions. But it will be best to employ the term *hormone* in the sense in which it is used by its inventor, i. e., to denote any substance in the blood which excites cells of the body to activity, and to

*The original expression employed by Bayliss and Starling (Journ. Physiol.) in their paper on secretine was "chemical messenger." This is more appropriate as a general term than "hormone" because it includes all chemical agents which produce an effect at a distance, whether such effect be excitatory or inhibitory. If, in place of "hormone," Starling had selected the expression "hermone" (Ἑρμῆς, Mercury), the difficulty which is caused by the use of the term "hormone," which implies excitation, for agents which act in exactly the contrary manner, would not be felt. Biedl distinguishes "erregende Hormonen" from "hemmende Hormonen," i. e., excitants which excite, from excitants which prevent excitation. It is true that he regards the one class as exciting katalobic changes and the other as exciting anbolic changes, but this is purely theoretical, and in many cases it is improbable that this is their mode of action.

denote by a special term those specific substances which are produced by the organs of internal secretion for the purpose of either exciting or restraining the activity of distant organs. Since the most characteristic feature of the action of these substances is the resemblance to the action of drugs, such as the vegetable alkaloids, I propose to employ for these specific substances the general title ''autacoid substances,'' or, simply, ''autacoids'' (ἀυτός, self, and ἄκος, a medicinal agent or remedy). I would accordingly define an autacoid as a specific organic substance formed by the cells of one organ and passed from them into the circulating fluid to produce effects upon other organs similar to those produced by drugs. Such effects are either in the direction of excitation, in which case the endocrine substances producing them may be termed *excitatory autacoids* and would come under the expression ''hormones,'' or in the direction of restraint or inhibition, in which case they may be termed *restraining* or *inhibiting autacoids* and be classed as ''chalones.'' And the action of an autacoid may be described as *hormonic* or *chalonic*, according to the kind of effect it produces.

Some autacoid substances appear to produce opposite results in different parts of the body. Thus the adrenine of the suprarenal medulla causes contraction of the plain muscle of the bloodvessels and inhibition of that of the intestines. But in both cases the action may be regarded as that of a hormone or exciting agent, for both effects are produced by stimulating the end substance of the sympathetic nerves. In extreme dilution (1 to 1,000,000 or less) in mammals, and in a less dilute form in birds, adrenine causes inhibition instead of contraction of the muscle of the bloodvessels. But this again may be produced by excitation of inhibitory nerve fibres by the more dilute solution, and if so the action would still be hormonic. Nevertheless, the possibility of the same autacoid substance acting under some circumstances as a hormone or excitant and under other circumstances as a chalone or depressant must be borne in mind. This indeed serves to illustrate the drug-like nature of these principles, for such inversion of action under different circumstances is known to occur with some alkaloids.

Groupings of the Chief Endocrine Glands.

The principal ductless or endocrine glands can be grouped under the three main heads of *thyroid apparatus, suprarenal apparatus* and *pituitary* or *hypophysial apparatus.* With regard to these groups, it is noteworthy that each of the organs forming the group is compounded of two distinct, but usually closely intergrown parts. Thus the thyroid apparatus is composed of thyroid proper and parathyroids; the suprarenal of cortical and medullary fine tissues; the pituitary of epithelial and

epithelio-neural portions. And in each case the functions of the two portions, so far as is known, appear to be in no way related, difficult as it is to believe that tissues so closely connected anatomically should have no sort of functional connexion. The close anatomical connexion is, however, sometimes absent, as with those parathyroids which are altogether detached from the thyroid and as with the paired bodies and the interrenal body of the Elasmobranch fishes. A close anatomical relationship without any known functional bearing is, however, not without examples in other organs, e. g., in the frog there exists a very intimate anatomical connexion of the suprarenal with the kidney, although there is no reason to believe that any special functional relationship obtains between the two.

It is further noticeable that in each of the above groups one of the two parts has a more evident and in a sense a more active function than the other. Thus the removal of the parathyroids occasions symptoms which are far more acute than those produced by the corresponding operation on the thyroid alone. And extracts of the medullary substance of the adrenals and of the posterior or epithelio-neural part of the pituitary have an immediate and striking effect on various tissues and organs when injected into the bloodvessels, whilst similar extracts of the cortical substance of the adrenals or of the anterior or epithelial part of the pituitary are without any obvious action. There is, however, in the case of the thyroid, direct experimental as well as clinical evidence, and, in the case of the suprarenal capsules and pituitary, the testimony of much clinical observation to furnish reason for the belief that the portions of these glands extracts which are inactive when injected into the blood may exercise, if a slower, yet a no less potent influence upon the organism than the portion the activity of which can be demonstrated by intravenous injection.

Methods of Determining the Functions of the Ductless Glands.

Two general methods are employed for this purpose, the one being the observation of the changes which result from partial or complete surgical removal of the organ in man and animals or its destruction by disease, and the other, observation of the changes which result from the administration of watery or saline extracts prepared from the organ. As has been already stated, the active principles of the endocrine glands are not destroyed by boiling with water or Ringer's solution, at least for a short time. Advantage is taken of this fact to prepare extracts which are free or almost free from protein or nucleo-protein, since the introduction of these substances into the blood might tend to mask the effect of the autacoid which is being tested. In this way solutions may be pre-

pared, and kept, after sterilization, in hermetically sealed receptacles almost indefinitely. Preserved in the dry condition also the autacoids appear to undergo no diminution of their activity. In these particulars animal autacoids resemble extracts of plants containing active medicinal principles of an organic nature, with the action of which, as has already been indicated, the effects they produce bear a close comparison.

The extracts can be administered by the mouth, or by subcutaneous, or intramuscular, or intraserous, or intravenous injection. The last mentioned method, viz., injection into a vein, being the most direct, is the one generally resorted to for the determination of their action. It was first employed to investigate the physiological action of such extracts in 1894, and led immediately to the discovery of the bloodpressure-raising principles of the suprarenal capsules and of the pituitary body.

Administration by the mouth.—This is well known to be effective in the case of the thyroid and the fact is taken advantage of in cases of hypothyroidism such as occurs in endemic goitre, cretinism and myxœdema. On the other hand, thyroid juice or the substance of the gland given freely with the food in normal individuals produces symptoms which are interpreted as due to excess of the thyroid autacoids in the blood. With smaller doses certain effects are produced upon metabolism, including an increase of N-secretion and an increase of O_2 intake and of CO_2 excretion, with the reduction of body fat. Buccal administration is stated by Cushing to yield good results with pituitary extracts or pituitary gland substance in cases of hypopituitarism, although in normal individuals no effect is apparent. Buccal administration of suprarenal extract also gives little result in normal individuals, but both in Addison's disease and in certain other affections beneficial effects have frequently been recorded when the extract has been thus administered.

Administration by subcutaneous or intramuscular injection.—As with drugs the effects of administering the animal autacoids by hypodermic injection are usually more rapid and more marked than with buccal administration. But in some cases the difference is not very striking so far as immediate results are concerned. If, however, extract of the medulla of the suprarenals or of the posterior lobe of the pituitary body are administered by intramuscular injection—absorption being promoted by gentle massage—they rapidly cause their characteristic effects (Meltzer and Auer). Probably the reason why these extracts when given by hypodermic injection produce little general result—although the local effects in causing vasoconstriction may be very marked—is that the autacoid is rapidly destroyed in the body; so that when absorbed slowly it is got rid of before any excess is able to accumulate in the blood. This

applies only to moderate doses and to the immediate effects. Secondary effects may be seen with large doses, and these may be of a marked character.

Intravenous injection. The immediate effects—if any—of the animal autacoids are, as with drugs, unfailingly exhibited as the result of the injection into a vein of the extracts containing them. In this manner can be shown the action of extract of thyroid in causing a marked but evanescent depression of the bloodpressure and in affecting the excitability of the depressor nerve: the various effects of extract of suprarenal medulla; such as contraction of bloodvessels with raising of bloodpressure, acceleration of the heart, sometimes preceded or followed by inhibition, flow of saliva, erection of hairs, dilatation of pupils, retraction of third eyelids, and protrusion of eyeballs, contraction of uterus, vas deferens and seminal vesicles, inhibition of gastric and intestinal movements and of the bladder: as well as those produced by extracts of the posterior lobe of the pituitary, such as contraction of the bloodvessels with slowing of the heart, increase of secretion from the kidneys, outflow of milk from the mammary gland, contraction of the uterus, of the intestines, and of plain muscle in general.

A caution must here be entered against the too hasty conclusion that a particular effect obtained in injecting an organ extract is a specific effect due to the autacoid substance. Especially is this warning necessary in experiments in which the bloodpressure is employed as the gauge of activity. For there are few organs which yield extracts that are absolutely inert when tested by intravenous injection. This applies to many glandular and lymphatic structures, extracts of which cause generally a rapid fall of bloodpressure, which is, however, usually speedily recovered from, but sometimes—as with kidney extracts—a more or less distinct and prolonged rise. The depressor effect seems often to be dependent upon the presence of nucleo-protein in the extract and is usually greater in proportion to the number of nucleated cells which the organ contains. Sometimes it may be due to the presence of choline. The pressor effect sometimes seen is also probably not specific. Whatever produces it is not of the nature of ordinary autacoids; it differs from these in being destroyed by boiling.

Extracts of various animal tissues—especially if unboiled—are liable to produce intravascular clotting. If this be general, instant death is the result; if localized, it may manifest itself by serious interference with the functions of the nervous system or of other organs: and the result of such injection might erroneously be set down to a specific action of the extract injected, although it would obviously only represent the result of an accident. A similar caution applies, although in a minor degree and for a different reason, to effects obtained as the result of buccal and hypodermic administration of animal-extracts, for such effects—especially differences caused by different extracts—may (unless they can be otherwise proved to be specific) be produced by variations in amount of such organic substances as nucleo-protein or other nutritive materials which may affect growth and metabolism, when added to the ordinary diet of animals.

LECTURE II.

THE FUNCTIONS OF THE THYROID APPARATUS.

This apparatus consists (1) of the thyroid proper, in the form of two lobes (generally united in man by an isthmus over the trachea) situated on either side of the larynx and windpipe, and (2) of the parathyroids; two on each side: one—the superior (parathyroid IV), which is usually in contact with the corresponding lobe of the thyroid near its dorsal aspect*, whilst the other—the inferior (parathyroid III), lies either in contact with the corresponding lobe of the thyroid at its ventral aspect or is removed a greater or less distance from it, sometimes as low down as the thymus.

The thyroid may contain embedded in its substance a portion of tissue resembling that of the thymus gland, and, like that, containing lymphocytes and corpuscles of Hassall. Such portion of thymus tissue is developed from the same branchial cleft (IV) as the superior parathyroid, whereas the main thymus is developed from cleft III. Accessory thyroids, usually quite small, occasionally occur in the tissues of the neck and in the anterior mediastimum.

Structure and Development of Thyroid.

The thyroid proper is an organ consisting of small closed vesicles of varying size and shape, but for the most part spheroidal. Each vesicle is lined by epithelium which is usually cubical; but the cells may be columnar or flattened in accordance with the state of distension of the vesicles. There is no definite basement membrane separating the epithelium from the connective tissue and bloodvessels. The vesicles are generally filled by the so-called "colloid," a viscid fluid in the fresh organ, which is coagulated into a solid substance by fixative reagents. The intervesicular substance is areolar tissue, containing in parts many small cells. Some of these are lymphocytes whilst others are not unlike those of the parathyroids, although the identity has not been established. There are also very numerous bloodvessels, the thyroid being one of the most vascular organs in the body, receiving in proportion to its size more than five times as much blood as the kidneys. The capillaries penetrate as far as the vesicular epithelium with which they come into immediate contact. There are numerous lymphatics within the organ, and "colloid" like that of the vesicles is said to be occasionally seen within them. The gland receives nerves from the sympathetic and from the vagus through the

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*In some animals this parathyroid is embedded in the substance of the lobe.

superior and inferior laryngeal: the nerves are distributed both to the bloodvessels and to the secreting epithelium.

The vesicles of the thyroid do not always present the appearance above described. Sometimes they are irregular, with projections of the wall into their interior, and are lined with pronouncedly columnar epithelium cells. In these circumstances there is usually little or none of the typical colloid material in the vesicles—although the appearance of the epithelium is that of marked secretory activity. It may be inferred that the secreted material finds in these cases a ready exit from the vesicles and thus fails to accumulate within them: it is possible that it may also be different in consistence and quality. So far as can be ascertained these differences of appearance are seen in animals which are otherwise normal. A glandular structure of this type, but even more pronounced, is noticeable in the thyroid in cases of exophthalmic goitre in man. It is usually interpreted as indicative of the production of excess of secretion (hyperthyroidism). The epithelium cells of the vesicles contain fatty granules which, according to Erdheim, increase in number with age: they are most numerous near the free border. The "colloid" is insoluble in alcohol, water, or either: when coagulated it is readily stained by eosin, less easily by haematoxylin. In fixed sections it often appears to be shrunken away from the epithelium. It is believed to be formed from granules which are produced within the cells and which become changed and dissolved on extrusion. Doubtless it contains the active principles of the secretion and probably forms a storehouse whence they can be extracted as required by the organism.

The "colloid" of the thyroid appears always to contain iodine. It is true that cases have been recorded both in man and animals in which a negative result has been obtained on analysis, but according to A. T. Cameron, this is probably due to the employment of methods of detection less sensitive than those now used.

The thyroid is found in all Vertebrata from Amphioxus upwards. It is originally developed in the same way as an ordinary secreting gland by a median outgrowth from the entoderm lining the floor of the pharynx at a level between the first and second branchial arches. It appears very early and grows backwards as a solid column of cells, bifurcating at the upper end of the trachea into two lateral portions. The solid column is hollowed out into a duct *(ductus thyreoglossus),* which presently becomes obliterated, usually completely; its original opening remains throughout life as the *foramen caecum* at the back of the tongue. The lateral parts into which the caudal end divides

branch again and again to form a system of hollow epithelium-lined tubes, and later these become cut up into the closed vesicles which are characteristic of the gland. In mammals they are joined by outgrowths from the ventral wall of the pharynx on each side behind the last branchial cleft (*post-branchial bodies*); these accordingly contribute to the formation of the organ, but to a very different degree in different species of animals.

Structure and Development of Parathyroids.

The *parathyroids* are four minute organs each averaging 6 mm. in length, and 3 to 4 mm. broad, and weighing 0.03 gramme (half a grain). Sometimes there are more than four, rarely less. As already stated, one or more may occur altogether detached from the thyroid, but usually in man they are closely attached to it: one may even be embedded in its substance. They were described by Sandstrom in 1888. Their physiological independence and distinction from the thyroid proper was recognised by Gley in 1891 and confirmed by Vassali and Generali in 1896, but is not fully accepted by Vincent and a few other authorities.

Each parathyroid is a mass of polygonal epithelium-like cells, arranged in strands or trabeculae with numerous sinus-like capillaries running between or around them. There is a capsule of areolar tissue sending in processes to join the interstitial tissue of the organ: plain muscle cells have been described in this: it may also contain fat-cells. Besides the ordinary cells of the gland—which are stained with difficulty by most dyes—others occur which contain oxyphil granules, staining intensely with eosin (Welsh): these only appear after the tenth year in man. Whether they represent a functional stage of the ordinary cells or not is uncertain. Both kinds of cells contain fatty granules; glycogen has also been detected in them.

Vesicles containing colloid material similar to those of the thyroid but usually smaller are frequently found in the parathyroids. They usually increase in number with age, and occasionally the colloid is found between the cells, not enclosed within a vesicle. Whether it is of the same chemical nature as that of the thyroid is not established. But it is noteworthy that after complete removal of the thyroid with those parathyroids which are embedded in it, the colloid-containing vesicles of the parathyroids which have been left were found by Vincent and Jolly to be increased both in number and size. This observation has been confirmed by Halpenny and Thompson, who have found that

if the animal survives a sufficient time these vesicles become large and irregular and present a close resemblance to those of a thyroid in superactivity, as in exophthalmic goitre. The same observers found that after removal of all the parathyroids the thyroid tissue itself may take on a similar appearance, with large and irregular vesicles. In this case there is also seen a multiplication of intervesicular cells, and these appear to be of the same nature as the cells of the parathyroids. The conclusion is that the tissues of the two organs are largely intermixed, at least in birds and mammals, although in lower Vertebrates Mrs. Thompson found the two to be completely separate both developmentally and structurally. Biedl has made a similar observation of the development of colloid-containing vesicles in the parathyroid in a case of atrophy of the thyroid in man.

The nerves of the parathyroids, like those of the thyroids, pass both to the vessels and to the secreting cells. Some evidence has been adduced by Asher and by Edwards which seems to show that the cell-activity is controlled by the nervous system.

The parathyroids are developed from outgrowths of the IIIrd and IVth visceral clefts on either side: from the same clefts the rudiments of the thymus are also derived; occasionally, as already mentioned, one or more outgrowths from the thymus rudiments pass into the thyroid. On the other hand parathyroid and even thyroid tissue occasionally occurs within the thymus: in some animals, e. g. the sheep, constantly.

Effects of Removal or Destruction of the Thyroparathyroid Apparatus.

Surgical or experimental removal of this apparatus (a) may be complete; or (b) may be confined to the thyroid, with or without those parathyroids which are embedded in its substance, the other two being left; or (c) may involve only the parathyroids, most of the thyroid itself being left. The results vary (1) with the nature and completeness of the operation, (2) with the species of animal, (3) with the age of the animal.

Effects of parathyroidectomy.—If the operation is complete, i. e. if it includes all four parathyroids—most animals die as the result of the removal; some within a few days, others within a few weeks. The most acute symptoms are exhibited by carnivora such as dogs, cats, foxes and wolves (Vincent) and the young of herbivora (v. Eiselsberg, Sutherland Simpson) and are of a nervous nature. For the first day or

two there are no symptoms, other than some loss of appetite. There then supervenes marked exaltation of reflexes, which leads to the occurrence from time to time of fibrillar contractions of muscles and later cramp-like and clonic contractions, and eventually convulsive fits; these may be of considerable violence and alternate with intervals of depression. The body temperature may rise two or three degrees (centigrade) during the fit. The paroxysms are usually accompanied by rapid gasping respirations which may be synchronous with the heart-beats; sometimes by vomiting and diarrhoea. Death may occur within a few days or the affection may last a long time and spontaneous recovery may occur. The syndrome is usually spoken of as ''tetany'' *(tetania parathyreopriva)*; which is in no way synonymous with ''tetanus.'' The fits are sometimes frequent but more often occur at long intervals; the animal, if it fails to recover from the effects of the removal, usually succumbs during a convulsion.

Tetany is without doubt due to the loss of the parathyroids, for it will occur when these alone are removed. It may take an acute or a chronic form and it varies greatly in severity. The symptoms may remain latent for a considerable time and only show themselves as the result of some unusual condition such as pregnancy. The effect is on the motor neurones, for Horsley and Lanz state that it is not influenced by ablation of cerebral cortex; nor, according to Mustard, by section of dorsal roots. After spinal transection it disappears below the level of the lesion, but the hind limbs may show rhythmic movements. In many cases it is relieved by administration of thyroid substance: it is uncertain if this result is due to included parathyroid alone. When tetany is produced by *total extirpation* of all parathyroid tissues it can apparently only be cured by a successful graft of a parathyroid from an animal of the same species. The condition has often been found to occur after complete removal of the thyro-parathyroid apparatus in man and may be sufficiently serious to threaten life, unless suitable measures are taken to combat the effects of parathyroid loss.*

In order to prevent the accession of tetany in operations for removal of thyroid tumours it is usually necessary to leave at least two of the four parathyroids.

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*A case in which all possible remedies, and grafts from various animals, including a monkey, were tried without avail, but which was rapidly and completely cured by the implantation into the subcutaneous tissue of a parathyroid obtained from the dead-house is described by W. H. Brown in the Annals of Surgery, Vol. LIII, 1911. Others have furnished similar records.

The most satisfactory explanation of the nervous results of the removal of the parathyroids is the assumption that they yield to the blood a special autacoid—presumably of a chalonic or restraining nature—which tends to prevent over-excitation or discharge of nerve-cells. It has been suggested that the over-excitation, since it occurs most markedly in carnivora, is induced by products of protein metabolism. Some species exhibit no symptoms whatever—at least when the operation is performed on the adult. Horsley stated that this is the case with birds and rabbits; but, according to Gley, the latter are affected if care is taken to find and remove all four parathyroids, and Doyon and Jouty obtained typical tetany in hens which had been parathyroidectomized. Vincent and Jolly found that rats and guinea-pigs do not seem to suffer from removal of their parathyroids, but Christiani and Erdheim both describe tetania parathyreopriva in rats: and Pfeiffer and Meyer obtained it in mice. According to Vincent and Jolly badgers are totally unaffected by complete removal of both thyroids and parathyroids.

It is possible that insufficient attention has been paid to age by many who have experimented on the subject. For it is certain that young animals are much more susceptible both to thyroidectomy and to parathyroidectomy than adults. This is strikingly exemplified in recent experiments by v. Eiselsberg and by Sutherland Simpson on sheep and lambs: the sheep showing no symptoms whatever, while the lambs exhibited both symptoms of tetany and arrest of development with supervention of cretinism. Adult goats on the other hand exhibit well marked tetania parathyreopriva. In monkeys this condition has most generally been missed, but it sometimes occurs.

Effects on metabolism.—An observation which has frequently been made after parathyroidectomy is the occurrence of changes in the growth and structure of the bones and teeth. Naturally these changes are only seen if the animals survive the operation for some time. In the teeth the calcification—especially of the dentine—appears to be delayed (young rats) and in the skeleton the bones generally remain smaller than in the controls: the healing of fractures is also said to be delayed. If these changes are the direct result of the removal of the parathyroids there is thus some reason for believing that these glands produce a second autacoid which is able to influence calcium metabolism, and a further foundation for this is met with in the fact that more than one observer has described an increase of calcium excretion in parathyroidectomized animals. In connexion with this subject but pointing in the opposite direction it is noteworthy that many

cases of osteomalacia have been found to be associated with hyperplasia (adenoma) of one or more parathyroids and therefore presumably with a condition of hyperparathyroidism.

MacCallum and Voegtlin found that the effects of parathyroidectomy could be removed by injection of extract of parathyroid. The extract has also been used with some success in man by Halsted. Extract of pituitary is said by Ott to have a similar effect. The same result was obtained by MacCallum from the administration of calcium salts, both subcutaneously and by the mouth. According to Biedl, however, these salts do not prolong life after the operation; and in my experience they may altogether fail either to prevent or alleviate post-operative tetany. According to Carlson and Jacobson, the action of calcium salts, when it occurs, is like that of other substances which decrease the excitability of the nervous system. No other substance appears to exhibit the specific action on the nervous system of the parathyroid autacoid.

Hyper-parathyroidism.—According to Ott extracts of parathyroid when injected intravenously have an entirely different effect from those of thyroid. He states that the blood-pressure is first raised, then lowered; that they increase the rate of respiration; that they are diuretic, acting directly on the renal epithelium, and that in large doses they have the effect of lowering the body temperature. Also that applied locally the extracts increase the extent of the contraction both of intestines and uterus, and dilate the pupil.

Clinical evidence. Various clinical symptoms have been ascribed to pathological changes in the parathyroids, which have been supposed to lead (1) in the direction of atrophy or diminished secretion (*hypo-parathyroidism*) or (2) in the direction of enlargement or increased activity (*hyper-parathyroidism*), or (3) in that of altered secretion (*dys-parathyroidism*). To the first condition have been ascribed manifestations resembling those of tetania parathyreopriva. These occur under various circumstances, e. g. during pregnancy, in the course of infectious diseases, and in *tetania neonatorum*. In some of these cases degenerative changes or haemorrhages have been described in the parathyroids. But other cases have been recorded in which changes of a similar character have been found post mortem in the parathyroids without symptoms of tetany having been noticed during life. Attempts have also been made to associate conditions showing increase of response to reflex or to cortical stimuli, e. g. such as occur in *Thomsen's disease* or in *paralysis agitans*, with a condition of chronic deficiency of parathyroid secretion. And on the other hand it has been suggested that pseudoparalytic conditions, such as those which are found in *myotonia paralytica* and *myasthenia gravis*, are due to chronic increase of the secretion. But the evidence in support of these views of the origin of such affections is by no means convincing.

The theory that the parathyroids serve the purpose of destroying poisonous products of metabolism which are elaborated in the main thyroid—apart from its *a priori* improbability—has received no support from the results of experiment. If the removal of the parathyroids were to be explained in this manner, simple parathyroidectomy should produce much more acute symptoms than total removal of the whole thyroid and parathyroid apparatus, but Biedl states that there is no difference in the acuteness of the symptoms. It is however possible that, as already stated, the symptoms of tetany may be produced by the accumulation in the blood of toxic intermediate products of protein metabolism, such as appear when the metabolic functions of the liver are interfered with. If this is so it might be inferred that the parathyroids produce an autacoid of hormonic nature which excites some other organ or organs (e. g. the liver) to complete the metabolism of proteins. But the simplest theory to explain the phenomenon observed is that already suggested, which assumes the production of a chalonic autacoid serving to diminish the excitability of nerve-cells. This hypothetical autacoid—which it must be well understood has never been isolated—may provisionally be termed *parathyrine.* We shall see that there is reason to believe that the main thyroid produces an autacoid with an opposite tendency.

The Effects of Removal and of Atrophy of Degeneration of Thyroid (Two or More of the Parathyroids Being Left).

Considerable variations are found with animals of different species and even with individuals of the same species. As with parathyroidectomy, thyroidectomy produces the most marked results in young animals. Similar results are obtained in cases of spontaneous atrophy of the gland, or when such a change in structure as interferes with its functions occurs in young children. There is arrest of growth, especially of the skeleton, the cartilage-bones long remaining incompletely ossified; development of the generative organs is much delayed; the integument is swollen, the surface of the skin dry; the hair thin; the face pale and puffy; the abdomen swollen; the nose depressed; the hands and feet are podgy. The fontanelles of the skull remain open. The muscles are limp and weak. Deaf-mutism is common. The highest functions of the nervous system remain undeveloped: this is due to an arrested development of cells of the cortex cerebri.

The above combination of symptoms forms the condition known as *cretinism.* This may be either sporadic or endemic; the former generally associated with absence of early atrophy of the thyroid; the

latter with goitrous degeneration: but the differential diagnosis is not always easy as most of the symptoms are similar. Of endemic cretinism, according to McCarrison, there are in the Himalayan valleys two types, the myxoedematous and the nervous: the latter is presumably associated with atrophy of parathyroids; whilst in the former the parathyroids are unaltered. This is the type chiefly met with in Europe. These symptoms do not, however, show themselves until some little while after birth, in spite of the absence of a thyroid. The absence appears to be sufficiently compensated for, for a time at any rate, by autacoids conveyed from the mother's thyroid to the child; before birth through the placenta, after birth through the milk. If the atrophy is congenital—in which case it usually takes the form of complete lack of development of the thyroid proper, the parathyroids being generally present and well developed—the condition of cretinsim and all the above symptoms are well marked.

If either thyroid atrophy is present or in the adult subject such degenerative changes take place in the gland as materially affect its functions, the condition known as *myxoedema* (or *Myxoedema adultorum* to distinguish it from the corresponding affection of the child) becomes manifested. This condition, which is much more common in females than in males, was described by Gull in 1873, and recognized by him to be a cretinoid condition of adult life; while, in 1877, Ord, who gave to the affection the name myxoedema—which was however based on a misapprehension—showed that it is associated with changes in the thyroid. It is characterized by thickening and swelling of the integument, which pits on pressure, the pitting disappearing on relaxing the pressure: by the skin becoming dry and the hairs falling out: by a low body temperature, and by mental dullness and general impairment of sensibility.* Both in spontaneous and in operative myxoedema the metabolic processes are diminished in activity so that although less food is taken the body weight may increase. Regenerative changes also occur more slowly. There is usually a considerable deposition of fat, especially under the skin. The activity of the sexual functions is diminished in both sexes. There is a diminution in the amount of oxygen consumed and in the amount of nitrogen excreted. There is increased tolerance for sugar and a considerably larger amount than usual (as much as 300 g.) may be taken without producing glycosuria. Nevertheless glycosuria occurs sometimes, but is not excessive.

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*Brun and Mott found in three cases of myxœdema in the human subject, general chromatolysis of nerve-cells of subacute character: they regard these changes as secondary to the thyroid affection.

Symptoms similar to those of myxoedema are produced as the result of surgical removal of the thyroid in man. This was first apparent as the result of the effects of operation for goitrous tumours (J. and A. Reverdin, Th. Kocher). The Reverdins indeed spoke of the condition as one of *post-operative myxoedema,* whilst Kocher termed it *cachexia strumipriva.* It begins to show itself at a variable period after operation—from a few days to months or even years—and is more readily produced in young than in older subjects. It is sometimes accompanied by symptoms of tetany: when present, these symptoms are presumably referable to involvement of parathyroids. According to Kocher, the patients rarely survive the complete loss of the thyroid for more than seven years. To prevent serious ill effects at least one-fourth of the organ must be left.

The above symptoms, whether due to congenital atrophy or to operative removal, can be allayed or entirely removed by successful implantation of pieces of thyroid (Schiff) an operation which has however rarely succeeded in man* or by administration of thyroid substance or extract either hypodermically (Murray) or by the mouth (Mackenzie and Fox). Patients suffering from the effects of loss of thyroid secretion, whether this take the form of cretinism, myxoedema or cachexia strumipriva, can be completely restored to health and kept normal for apparently any length of time by buccal administration of the gland or its extracts. If the treatment be intermitted the symptoms almost at once begin to reappear. The effects are therefore obviously due to the loss of the autacoid contained in the internal secretion. This autacoid actively influences the metabolic processes of the body, either directly or indirectly promoting the nutrition of certain tissues, especially the connective tissues and the tissues of the nervous system.

Effects of Diminution of Thyroid Secretions: Hyperthyroidism.

Enlargement of the thyroid such as occurs in endemic goitre, in spite of a great increase in volume of the gland, is commonly not attended by symptoms of hyperthyroidism, but the reverse. Sometimes such enlargement is the result of malignant cell-proliferation (carcinoma or sarcoma); in this case the functions of the organ are as a rule still

*Kocher has, however, lately published 93 cases of attempted transplantation, 23 of which were cured as the result of the operation and 18 showed improvement, although thyroid feeding had to be continued to some extent.

carried on.* The enlargement of the gland in endemic goitre generally takes the form of a diffuse hypertrophy: the follicles enlarge and their epithelium proliferates: new follicles also become formed. There is nearly always a tendency for the colloid to accumulate. This ultimately causes distension of the vesicles and flattening of their epithelium, which may eventually undergo almost complete degeneration. A characteristic degeneration of the arteries of the gland has also been described.

Whilst the above are the usual changes found in endemic goitre, many exceptions are met with. One would expect from the above description that the enlarged gland was yielding an excessive amount of secretion, and as a matter of fact, endemic goitre is occasionally characterized in its early stages by symptoms suggestive of hypersecretion and resembling some of those seen in incipient exophthalmic goitre. More often these symptoms of hyperthyroidism are absent: generally from the first, and always eventually, the appearances which show themselves are unquestionably symptomatic of hypothyroidism. This must mean that even if the secretion is being produced in abundance it is not of a normal character, the normal autacoid being either absent or deficient in quantity. Possibly the enlargement of the gland represents an attempt by nature to compensate for such deficiency.

Effects of Increase of Thyroid Secretions: Hyperthyroidism.

The effects of a too great amount of the thyroid autacoids in the circulating blood can be investigated either by their introduction directly into the circulation or indirectly by other channels such as the alimentary canal; or by studying the symptoms of those affections in which there is reason for believing that an excess of these autacoids is being secreted by the gland.

The immediate results of intravenous injection are relatively slight. The most common effect is to produce a marked but evanescent fall of blood-pressure, which is mainly due to dilatation of the peripheral vessels, complicated in some animals (cat) by an excitation of the vagus centre and consequent slowing of the heart. Whether these particular effects are specific is uncertain; at any rate somewhat similar results are obtained from many other organ extracts. According to

*It is a significant fact in connexion with the genesis of malignant tumours that when in such cases the whole of the gland is removed by the surgeon, should there be any metastatic growths elsewhere, e. g. in the liver, the usual symptoms of cachexia thyreopriva do not show themselves (v. Eiselsberg).

Lohmann and others the depressor substance in thyroid extract is cholin. Asher states that the fall of blood-pressure and effects on the heart are not seen in the rabbit, but other results are produced, for immediately after such injection in that animal the excitability of the vagus and of the depressor nerve is increased, and the changes in blood-pressure, pupil, etc., produced by a particular dose of adrenine are enhanced. Given by the mouth in the human subject thyroid extract produces lowering of the blood-pressure.* Large doses are followed by tachycardia (rapid pulse), often with some irregularity; nervous excitability; flushing of the skin, with feeling of heat; increase of perspiration; and increase of nitrogen metabolism. If long continued the fat of the body is diminished and glycosuria may be caused. Alimentary glycosuria is also more easily produced than normally. In extreme cases there may be exophthalmos and other effects referable to cervical sympathetic excitation, such as dilatation of the pupil and (in animals) retraction of the third eyelid; psychical excitement; sleeplessness; tremors of the limbs; in short, most of the symptoms of exophthalmic goitre. The addition to the food of animals of even a small amount of thyroid gland has the effect of increasing nitrogenous metabolism, as shown by the increase of nitrogen in the urine. This is accompanied by a corresponding increase in food consumption. Some of the additional nitrogen thus ingested is retained in the body but this is compensated for by increased fat consumption, so that the difference in growth curve of the thyroid-fed animals and the controls is but slight. With large doses of thyroid there soon ensues marked loss of weight due to increased nitrogenous excretion and loss of fat.

The colloid contents of the thyroid vesicles are greatly increased during the ingestion of much thyroid substance.

Exophthalmic goitre.—This affection, first described by Parry (1825) and associated by him with the thyroid, is also associated with the names of Graves (1835) and Basedow (1840), both of whom called special attention to the symptoms. The name *exophthalmic goitre* expresses its most prominent sign. The disease is associated with enlargement of the thyroid. According to Moebius and Greenfield the enlargement is accompanied by hypersecretion which is the direct cause of the symptoms, this opinion being founded on the fact that (1) as has just been mentioned, some of the symptoms of the disease can be produced by excessive administration of thyroid, and (2) that the symp-

*In diabetic subjects it is said to cause the opposite result—an effect lasting for several days.

toms are for the most part opposite in character to those which are known to be produced by atrophy or diminution of function of the gland. Thus there is a rapid and often irregular pulse; nervous and psychical excitation, with muscular tremors; a feeling of warmth in the skin, and throbbing of cutaneous vessels, often accompanied by profuse sweating; shallow respiration; markedly increased metabolism (especially nitrogenous) with abnormal appetite and loss of body fat; a decreased assimilatory power for carbohydrates; an anxious restless expression; prominence of the eyeballs;* wide palpebral aperture, often with dilatation of pupils. The enlargement of the thyroid may involve only one lobe. The enlarged gland pulsates, and gives a murmur on auscultation.

Exophthalmic goitre is far more common in the female than in the male (as 4.6 to 1), a fact which may be related to the enlargement of the gland, which usually occurs in the female at puberty and during pregnancy. It is generally associated with a persistent thymus, an internal secretion from which has by some authors been credited with the production of certain of the symptoms of the disease. About 13.5% have polyuria without sugar. Only 2% have glycosuria, although alimentary glycosuria is not uncommon. Albuminuria is present in about 11%.

The histological appearances are conformable with the theory of a hypersecretion (which may however be abnormal). The gland is greatly enlarged, and the individual vesicles are larger than usual and tend to run together. The interstitial tissue is increased in amount and assumes a lymphoid appearance, often with characteristic germinal centres. The follicle wall tends to grow into the interior of the enlarged and conjoined follicles in the form of ridges and papillae, thus increasing the surface for secretion and giving the cavities an irregular aspect. On the other hand, some follicles undergo retrograde changes, and may even disappear. The cells lining the follicles acquire a columnar form: in later stages they may undergo degeneration and become set free within the follicles. The contents of the follicles are more fluid than in the normal thyroid and stain less.

Direct proof of hypersecretion is thought to be furnished by the experiments of Reid Hunt, who found that the blood of a person afflicted with exophthalmic goitre increases the resistance of mice to

*It is stated that the exophthalmos may be unilateral, in which case it can hardly be produced entirely by the circulation of an autacoid in the blood without the intervention of a nervous factor.

the poisonous effects of acetonitrile; a reaction he had previously found to take place after injection of thyroid extract. Asher and Flack have also obtained physiological evidence of the existence of excess of thyroid secretion in the blood in this disease. Others, on the contrary, have found that injection into animals of serum from a patient in whom the disease is active does not produce the same effects as thyroid juice; and although in dogs small doses of extract from an exophthalmic goitre cause increased rate of heart-beat and some rise of blood-pressure, this is soon followed by the opposite condition. Moreover the action of the sympathetic is sometimes lessened and that of the vagus may be reversed. The symptoms are therefore produced, according to Gley and Sahli, not by excess of normal thyroid secretion circulating in the blood, but probably as the result of the production of a perverted secretion (dysthyroidism).

The Nature and Mode of Action of the Autacoid Substance Contained in the Internal Secretion of the Thyroid.

The active principle of the thyroid has been usually assumed to be represented by the non-proteid nitrogenous material known as iodo-thyrin or the compound proteid iodo-thyro-globulin. The former was prepared from thyroid by Baumann (1895) and found by him to contain a marked amount of iodine (.3 to .9 per mille of dry substance). In confirmation of this view the experiments of Reid Hunt and others seemed to show that the production of the autacoid is promoted by administration of iodides and that there is a certain relation between the physiological activity of the gland and its iodine content. But the fact that even when the dessicated thyroid contains a considerable amount of iodine it is sometimes found to have no action suggests that Baumann's substance is not the actual autacoid, although it may be associated with it. We are in fact still in the dark so far as the true nature of this autacoid is concerned and it seems better to express our ignorance by a term which implies no theory, leaving the question of its identity with iodo-thyrin or iodo-thyro-globulin open. I propose therefore provisionally to apply the word *thyrine* to denote the active principle, whether it be identical with or contained in the iodo-thyrin of Baumann or not.

As we have already seen, the autacoid of the parathyroid (parathyrine) is probably of chalonic, i. e. of inhibitory nature, serving to keep in check the activity of nerve-cells. On the other hand, the autacoid of the thyroid (thyrine) acts like a hormone in increasing

the excitability of nerve-cells. This increase of excitability is especially well marked in connexion with the sympathetic. Here the question arises: Is this a direct effect on the sympathetic system or is it indirect through the adrenals? which are stimulated to increased secretory activity by excess of thyroid in the blood. The answer is not easy. But it may be stated that although certain symptoms of hyperthyroidism are similar to those produced by excess of adrenine in the blood, others are not so. This is the case with the flushing of the skin, which is due to vascular dilatation; whereas adrenine ordinarily produces vasoconstriction. Further, excess of adrenine in the blood leads to glycosuria, which is not as a rule seen in exophthalmic goitre. Moreover it is undoubtedly the case that the administration of adrenine exercises a markedly beneficial effect in some cases of exophthalmic goitre: a fact which would be inexplicable on the theory that the results of hyperthyroidism are simply due to excitation of the suprarenals and the production of an excess of adrenine.

But although many of the effects of thyroid feeding and of hyperthyroidism otherwise produced can be explained by the presence of excitatory or hormonic autacoids, it is not possible to explain the results produced by thyroid deprivation, or hypothyroidism, upon the body generally and certain organs in particular merely by assuming the absence of these excitatory substances. For loss of the thyroid is followed by increased growth and presumably activity in certain organs. This is notably the case with the pituitary; and although it has been suggested that this a case of vicarious increase of size associated with the performance of similar functions, the similarity of the functions of the two glands is far from obvious. A more probable explanation is that besides a hormone which excites nerve-cells, the thyroid secretes an autacoid of chalonic nature which restrains the activity of certain other organs, such as the pituitary: on removal of the thyroid this restraint is abolished, and over-activity is the result.

The thyroid autacoids also affect the growth of the thymus gland, which has been found to undergo an increase in size in foetal animals after thyroid feeding of the pregnant mother (guineapigs): on the other hand the suprarenal capsules and the thyroid itself have been found to undergo a diminution in weight under these circumstances. Hoskins, who furnishes this observation, ascribes the effect upon the growth of the thymus to stimulation by a hormone furnished by the thyroid: if this is so, the opposite results on suprarenal and thyroid should be ascribed to an autacoid of opposite sign. In conformity with this idea the diminished growth of the skeleton and of the gen-

erative organs which follow thyroid removal in young animals should be put down to the absence of a hormone, which promotes their development.

A close relationship exists between the size and structure of the thyroid and the state of general nutrition of the animal. The effect of variations of diet upon the thyroid has been studied in rats by Chalmers Watson, who has shown that all transitions from an active or superactive organ with highly developed columnar epithelium and irregular large vesicles and without any great accumulation of colloid, to a gland with flattened epithelium and large spheroidal vesicles distended by deeply staining "colloid" are exhibited under the influence of different nutritive substances in the diet: the former conditions being, in the rat, typically seen when the animals have been fed upon a mixed food such as bread and milk: the latter when the diet has been composed of lean meat. Prolonged feeding of rats with lean meat led eventually to a shrinking in size of the vesicles and of the whole organ, these changes being associated with dryness of skin, falling off of hair, and other evidences of ill health; but in carnivora results of this kind were not observed.

Interaction of the Thyroid with Other Organs.

The generative organs.—The important influence exerted by the thyroid secretion on nutrition generally is no doubt responsible for the fact that hardly any organ in the body remains unaffected as a result of its complete removal or atrophy. But the secreting organs with which it may be regarded as being more specifically associated are few. Among them are the generative glands. In the female the thyroid becomes enlarged at puberty, during the menses, and during pregnancy. In the young thyroidectomized subject the generative glands are only slowly or imperfectly developed, the resulting condition being characteristically one of sexual infantilism. In the adult animal (dog) Alquier and Theuveny found diminished activity so far as production of spermatozoa is concerned, but less distinct evidence of change in the ovary; although the animals appeared to come on less completely in heat and to conceive with difficulty.

The liver and pancreas.—Other effects, of a more or less specific character, are produced upon liver-glycogen. Krause and Cramer find that in the cat and rat, fed with thyroid, glycogen disappears from the liver; but there is no glycosuria, the sugar having been conveyed to the tissues and oxydised. Parhon has obtained a similar result with

the rabbit. The thyroid therefore produces mobilisation of carbohydrates. Thyroid feeding also tends, as we have seen, to diminish the limit for the assimilation of sugar—this may be due to an increase in the secretion of adrenine, or perhaps to a direct inhibitory effect on the internal secretion of the pancreas.

After thyroidectomy the assimilation limit for sugar is markedly raised: and according to Eppinger, Falta and Rüdinger, adrenine-glycosuria is greatly diminished or fails to show itself. This statement has, however, been denied by Underhill and Hilditch. If the parathyroids be included in the removal the assimilation limit for sugar is lowered and adrenine produces a stronger glycosuria than in the normal animal. The influence of the thyroids and parathyroids is therefore antagonistic in this as in some other respects. According to Lorand, if a dog deprived of pancreas and exhibiting glycosuria be thyroidectomized the sugar disappears from the urine. Lorand further states that extirpation of the pancreas has the effect of increasing the amount of colloid in the thyroid vesicles and that thyroidectomy causes a marked increase in the amount of islet tissue in the pancreas. But both these statements are difficult to accept on account of the differences which are normally present, both in amount of colloid in the thyroid and in number of islets in the pancreas. If substantiated they would show a direct correlation between the thyroid and the pancreas, the internal secretion of the thyroid being restrained by that of the pancreas and the internal secretion of the pancreas by that of the thyroid, so that when either gland is extirpated, the internal secretion of the other either becomes more active or is increased in amount.

The adrenals.—There is, however, an indirect way in which the internal secretion of the pancreas can be influenced by thyroid secretion, and that is by the effect which the secretion produces upon the activity of the secretion of the suprarenal capsules. This effect is, as Asher and Flack have shown, in the direction of increase of excitability of those tissues, which are amenable to the action of adrenine. And when the thyroid is extirpated the activity of the secretion of the suprarenals is diminished. Not only is this the case with the effects of adrenine, but the phenomena generally which are normally produced by sympathetic stimulation are similarly affected. Further, with hyperthyrosis such as occurs in intense thyroid feeding and exophthalmic goitre most but not all of the symptoms are, as we have seen, those of over-excitation of the sympathetic and are similar to those caused by adrenine. Moreover, there is some evidence that the amount of adrenine in the blood is increased in hyperthyroidism as well as that its activity is enhanced.

Ott and Scott got increase of adrenine in the blood after intravenous injection of thyroid extract. They obtained, however, a similar result after injection of other organ extracts. Kraus and his fellow workers observed dilatation of the pupil of the excised frog's eye when placed in blood-serum or blood-plasma of patients affected by exophthalmic goitre, although blood-plasma of normal individuals does not give this reaction. But the fact that some cases of exophthalmic goitre benefit by the exhibition of adrenine is difficult of explanation, since from what has been stated this should cause an exacerbation of the symptoms. Moreover, it must be borne in mind that some of the physiological tests which have been used for adrenine would also be given by pituitrine, and this may be a factor in the discussion of the question. Kraus has also obtained chemical evidence of the presence of excess of adrenine in blood after injection into animals of the juice of thyroid gland from cases of exophthalmic goitre, and in such cases its presence has also been demonstrated by physiological tests (Fraenkel with the uterus; Trendelenburg and Bröking, with the frog's bloodvessels). It may therefore be assumed that the secretion of the thyroid in exophthalmic goitre acts as a direct stimulant to the suprarenal capsules, causing them to yield adrenine to the blood in larger quantity.

The pituitary body.—As has been pointed out above, a very striking effect is caused by removal or atrophy of the thyroid upon the pituitary body: which not only undergoes general enlargement but also exhibits well marked indications of increased secretion. These changes will be described when the pituitary is dealt with.

The thymus gland.—Reference has already been made to the anatomical and developmental relationship between thymus and thyroid, to the effect of thyroid feeding of a pregnant animal upon the growth of the thymus of the foetus, and to the supposed effect of the thymus in assisting to produce the symptoms of exophthalmic goitre: indeed its removal by operation has been recommended and even practised in that affection. In view of these circumstances some believe that there exists a mutual relationship between the two organs, and that they exercise—by their internal secretions—some sort of excitatory influence upon one another. In conformity with this it has been pointed out that the increase or diminution in size of the two organs usually go hand in hand. But this can only be early in life, for under normal conditions of growth and development the thymus is undergoing retrogression whilst the thyroid is becoming more active in its functions. Moreover, the variations in the thymus are so considerable,

and at present in spite of many observations so little is accurately known regarding the conditions under which they occur that it will be wise to reserve judgment as to the mutual relations of this organ and the thyroid.

Influence of the Nervous System on Thyroid Secretion.

It was shown by Cyon that vasodilator nerve fibres pass from the recurrent laryngeal nerves to the thyroid gland. Ossokin finds the gland to be supplied by both laryngeal nerves and also by the pharyngeal branches of the vagus. Vasoconstrictors pass to it by way of the sympathetic. H. Wiener found extirpation of the inferior cervical ganglion to be followed by atrophy of the gland and diminution of thyro-globulin in the thyroid of the same side. It has further been shown by Asher and his fellow workers that the internal secretion of the thyroid is directly influenced by the nerve fibres which pass to the gland by the superior and inferior laryngeal nerves. In order to test the amount of its autacoid in the blood they took advantage of the fact that injection of thyroid juice or extract into the circulating blood (1) increases the excitability of the vasoinhibitory fibres of the depressor nerve—or at least increases the effect produced by their excitation; (2) increases the effect of stimulating the splanchnics; (3) increases the effect of stimulating the cardiac vagus; (4) increases the effect produced by injection of a given dose of adrenine. They obtained these results during stimulation of the peripheral cut ends of the laryngeal nerves, but failed to get them if they had previously extirpated the thyroid. It has also been stated that the iodine content of a thyroid lobe is diminished as the result of excitation of the vagus of the same side.

These observations indicate that in the secretion and outpouring of its active principles the thyroid is, like externally secreting glands, under the direct influence of nerves. This fact serves to corroborate the conclusion arrived at from other considerations, that in this gland as in the parathyroids we have to deal with an organ of internal secretion. The view which was at one time held that its function is merely that of a destroyer of toxic substances circulating in the blood is no longer tenable. The same may be said for an old idea—renovated by Cyon—that the gland serves as a kind of shunt to regulate the flow of blood in the cranial cavity. This, indeed, has nothing to support it beyond the extreme vascularity of the gland and its position in close connexion with the carotids.

LECTURE III.

THE FUNCTIONS OF THE ADRENAL APPARATUS.

The suprarenal capsules or adrenals have received special attention, both from clinicians and physiologists, since Addison (1855) described the symptoms of the disease which bears his name and which he associated with degeneration of these organs. Addison's disease is characterized by great languor and general debility, with weakness and diminution of tone, not only of the skeletal but of the vascular and visceral musculature, feeble action of heart, loss of appetite, disturbance of the digestive tract, severe abdominal pain and extreme emaciation. Anaemia, which is an occasional accompanyment of the disease, was regarded by Addison, when it occurs, as symptomatic; but it is probably the result not of the destruction of the capsules but of the intercurrent affection (generally tuberculosis), which has produced their destruction. The most striking characteristic of the disease as described by Addison was undoubtedly the pigmentation (bronzing) of the skin, which occurs as a diffuse colouration upon the face and hands and other exposed parts and is increased in regions where there is some pigmentation normally present, such as the areolae of the nipples and the external genital organ. It is also found on the mucous membrane of the mouth and on that of the conjunctiva. Sometimes the bronzing does not occur; these cases are usually the more acute. The disease is fatal. Its course may be prolonged, "even to six or ten years. In rare instances recovery has taken place, and periods of improvement lasting many months may occur" (Osler). Some cases are markedly benefited by administration of suprarenal extract *per os* or hypodermically; others not at all.

The cause of the excessive formation of pigment is not understood, but it has been suggested (by Adami and others) that adrenine may be derived from the same source as the melanin of the skin and that if the formation of adrenine is interfered with an excess of melanin is formed and deposited. Meirowsky states that in portions of skin removed from patients who have died of Addison's disease an increase of pigment occurs as long as five days after death if the pieces are kept in a warm, moist chamber, but that this does not occur in the skin from those who have died from other causes. He suggests that a colorless precursor of the melanin is present in the skin, and supposes this to become transformed under the influence of light. Somewhat similar observations have been made by Königstein and by Biedl and Hofstätter, on the skin of dogs deprived of their suprarenal apparatus: but negative results were obtained with rabbits and other rodents. In epinephrectomized animals pigmentation of the skin is not seen: it therefore probably requires a gradual destruction such as occurs in chronic disease of the capsules in man, a condition

which has not hitherto been successfully imitated in animals. Some observers have, however, described pigmentation of the skin and mucous membranes in animals as the result of removal of the adrenals, or as the result of removal of one and injury of the other. But the evidence of the production of pigmentation by the operation is inconclusive.

Structure of the suprarenal capsules.—It is well known that the adrenals consist of two parts, which although anatomically united in many animals, are morphologically distinct and are developed from different embryonic formations; the first, known as the cortex, being formed from mesoderm-cells of the genital ridge, whilst the second or medulla is developed from cells which belong to the same neuroblast-masses as give rise to the nerve-cells of the sympathetic ganglia. In fishes for the most part these parts remain separate, forming the so-called *inter-renal body* or *bodies,* representing the cortex of the mammal, and the *paired chromaffine bodies,* representing the medulla. But in all higher vertebrates the two parts are united into one organ which is generally closely attached to the kidney on each side. In birds and reptiles the renal and adrenal tissues interlock; it is only in mammals that the same condition is found as in man, viz., a central medulla with an enclosed cortex.

Accessory suprarenals are not infrequent. They consist either of cortical substance alone, or of medullary substance alone, or of the two combined. They occur most commonly between the kidneys and along the lower part of the abdominal aorta as far as its bifurcation. In the male rat such an accessory gland is almost constantly seen close to the epididymis. They are relatively longer and more frequent in the new-born animal than in the adult, in which they may be missed altogether. The possibility of their presence must, however, be borne in mind when considering the results of the extirpation of the adrenals in animals.

Shielding of the Cortical or Interrenal Part of the Adrenal.

The *cortex* of the adrenal is composed of epithelium-like polygonal cells arranged mainly in columns *(zona fasciculata),* but near the medulla as a network of trabeculae (*zona recticularis*). Towards the surface the cell columns end in rounded and sometimes hollowed out terminations forming the so-called *zona glomerulosa,* the cells of which sometimes have a columnar form. The cells are usually rather larger in the *zona fasciculata* than in the other parts. Characteristic of the cortical cells is the presence of lipoid granules, which may give a yellowish colour to this part of the capsule. The *zona recticularis* contains also pigment granules which in some animals give it a distinct brownish colour. The human foetus is well known to have unusually

large suprarenal capsules. It has been shown by Elliott and Armour that the increased size is almost entirely due to a great development of a innermost part of the cortex lying at the boundary with the medulla (*boundary zone* of cortex).*

Its cells differ from those of the rest of the cortex in having no lipoid granules. After birth they undergo a fatty change and the layer gradually disappears, so that it is no longer distinguishable after the first year. At birth what will be the cortex of the adult gland consists only of a thin peripheral layer of cells containing lipoids; these cells multiply and the layer enlarges *pari passu* with the disappearance of the boundary zone. A remarkable fact pointed out by Elliott and Armour is that in the anencephalous foetus the boundary zone is absent and the suprarenal resembles that of other foetal mammals.

Functions of the Cortical Part.

Little is known regarding the functions of the cortex. Its anatomical relation in mammals to the chromaffine part and the fact that its blood passes directly into the medulla suggests that its cells may be concerned in the production of materials which are utilized by the medulla, but as has been above mentioned, this relation fails in many vertebrates. It has been stated by Abelous and others that the cortex contains a precursor of the adrenine of the medulla and that if left standing for twenty-four hours in an incubator a considerable amount of a substance giving the reactions of adrenine accumulates within it. But according to the investigations of Bayer the results obtained are not ascribable to adrenine, but to the products of protein decomposition. The statement that the cortex becomes enlarged during pregnancy and is small in cases of deficient sexual development seems to give evidence of some relationship between it and the generative glands; but whether this is direct, or operates through other ductless glands—such as the thyroid and pituitary—is not known. The close connection between the development of the sexual organs and that of the suprarenal cortex has been especially insisted upon by Glynn.

It has also been suggested that a function of the cortex may be to neutralize deleterious products which are formed in the process of metabolism of other organs or are introduced from outside. But this supposition has received no support as the result of experiments.

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*Not to be confounded with the "intermediate zone" of Virchow, which is a very thin layer, pigmented in old age, lying at the junction of the cortex and medulla.

One of the most striking facts connected with the cells of the cortex is their richness in lipoids and fats, which have been chemically investigated by many workers. Biedl (Innere Sekretion, Vol. II, p. 60, of 2d Edition) gives the following figures from his own investigations. The suprarenals of the pig yielded 74.61 per cent of water and 25.39 per cent of dry residue. Of the latter, 61.12 per cent consisted of proteins, etc., and 38.88 per cent of lipoid—besides some insufficiently distinguishable extractices. In this analysis the medulla was included, and as this is poor in lipoids the lipoid contents of the cortex must have a much higher value: far higher than any other non-nervous tissue.

Their microscopic appearances have been described by Elliott and Tuckett, who found, as others had before them, that besides granules of what appear to be fat, a doubly refracting substance is found in the cortical cells of most animals—varying in amount and in its position in the cortex in different species. In some it takes the form of doubly refracting crystals. Elliott and Tuckett regard both the fatty and the anisotropous substance as products of secretion of the cells. They find that the doubly refracting substance increases in amount during rest and diminishes as the result of muscular activity. But they state that in some animals, e. g. the sheep, both substances may be absent. In the guineapig there are numerous brown colored granules in the cells—chiefly in the *zona reticularis*—and Elliott and Tuckett state that these also accumulate during rest and quickly disappear with muscular work, fatty globules taking their place. The doubly refracting lipoid substances seem to consist mainly of lecithin and cholesterin—the latter in the form of esters. According to Orgler, they consist mainly of protagon. Rosenheim and Tebb, on the other hand, extracted from the suprarenal cortex of the ox various fatty acids, cholesterin esters and phosphatides, such as sphingomyelin, but not free cholesterin. It is probably of cholesterin esters that the doubly refracting material is mainly composed (Aschoff).

The suggestion that the suprarenal cortex may be the chief seat of manufacture of the lipoids of the body and may especially be related to the formation and development of the myelin of the medullated nerve fibres seems an obvious one. And the fact that in the human foetus and infant so large a development of suprarenal cortex occurs—which is missed in the anencephalous monster—seems to indicate a connexion between the development of the substances formed in the cortex and those constituting the cerebral hemispheres. But against this idea we have the further statement of Elliott and Armour that in the foetus the superadded part of the suprarenal cortex does not contain the doubly refracting lipoid substances which are characteristic in most animals of the ordinary cortical cells—although they speak of the cells of the foetal cortex as undergoing a fatty change after birth. Nor does the doubly refracting

lipoid matter occur in all animals: in many species it is absent altogether. This is the case with all adult ruminants examined, although it may occur in them in the young state. Thus while absent in the ox or cow it is said to be present in small amount in the calf. In both man and animals where normally present it tends to disappear under various abnormal (disease) conditions: whilst during pregnancy lipoids are said to increase in amount, not only in the suprarenals but in all other organs of the body.

The cortex increases in proportion to the growth of the body more than the medulla. It varies in size with the condition of activity of the sexual glands in animals; nevertheless, castration is followed by hypertrophy of the cortex. But there is no evidence that any kind of active autacoid substance is produced by the cortical cells, and it is probable that their function is associated with the building up of metabolic products which are to find employment in other parts of the organism.

Structure of the Medulla or Chromaffine Part of the Adrenals.

The *medulla* is composed of cells which have a different form and structural appearance from those of the cortex. They are arranged in what in section appear like anastomosing columns with spaces between, but in point of fact the medulla is better described as a solid cell-mass permeated by sinus-like capillary and venous spaces. In this respect it is not unlike liver tissue. Many of the cells are compactly arranged around vascular spaces. They are irregularly polygonal in form, but where they abut on the sinusoid spaces they often assume a more columnar aspect. There can be little doubt that the materials they secrete find their way directly into the blood within these spaces. The cell protoplasm contains granules which vary in amount in different cells. Some of these granules are stained brown with chromic acid and its salts (*adrenine* or *chromaffine reaction*) and this gives a yellowish-brown color to the medulla when the suprarenals are fixed in any solution containing these salts. Occasionally the coloration is more diffuse. A similar reaction is sometimes given by the blood and lymph in the vessels of the medulla in sections of the organ.

Besides the chromaffine granules above mentioned, others are found, somewhat coarser, soluble in water and alcohol but not in ether, and staining with difficulty. Lipoid and pigment granules are also sometimes seen. The relationship of these various granules to one another is not known. Those accessory glands which have a similar structure and derivation to the medulla of the suprarenal capsules and contain cells which are colored brown by chromic acid are termed *paraganglia* by Kohn, *chro-*

maphil bodies by Vincent, *chromaffine bodies* by most other authors* This last term—although not without objection on the score of etymology—has come to be so widely employed to express the specific character of the organs in question that it seems necessary to adopt it.

All the physiological effects which are about to be described as yielded by suprarenal extracts are obtainable from extract of medulla alone: intravenous injection of extract of cortex gives no appreciable result. In Teleostei, where the cortex is represented by the corpuscles of Stannius, and in the Elasmobranchs, in which the cortex is represented by the interrenal body and the medulla by the entirely separate "paired bodies" of Balfour, it has been shown by Vincent that the latter yield an active extract, whilst that of the other bodies is inactive. It was early proved by Moore that the action of the extracts of medulla is due to the material within the cells which becomes stained with chromic salts and which is readily oxidized by various reagents, giving characteristic color reactions with ferric cholride, chlorine water, and caustic alkalines (Vulpian). A similar reaction was obtained by Vulpian with a material contained in the blood of the suprarenal vein. This chromaphil substance, after being partly isolated by Fränkel, was prepared in a condition approaching to purity by v. Fürth, and by Abel, and eventually in a crystalline form by Takamine and by Aldrich. It has received various names, such as *suprarenin* (v. Fürth), *epinephrin* (Abel), *adrenalin* (Takamine), the last being that by which it is most widely known. But as this name has a commercial attachment, it is better to employ the neutral expression *adrenine* in place of it.** It has been estimated by Batelli that the suprarenal capsules contain about 1 part of adrenine per 1,000 of the whole gland, but as it only occurs in the medulla, which forms less than a fourth of the gland, the proportion in this would be proportionately greater.

Adrenine can be synthetized, methyl-acetyl-pyrocatechin being first prepared. This when reduced gives a racemic salt which can be split into *d*-adrenine and *l*-adrenine. The latter appears to be in all respects identical with the natural product, while the racemic salt and its dextrorotatory moiety are much less active physiologically.

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*The carotid gland is of this nature. The coccygeal gland is different. It contains no chromaffine cells and appears to represent an arteriovenous anastomosis which is met with in certain lower mammals. The paraganglia invariably occur in close morphological and developmental connexion with sympathetic nerves and ganglia (Stilling).

**Chemically adrenine is *ortho-dioxyphenol-ethanol-nethylamine* and is related to tyrosine.

Chromaffine cells containing an adrenine-like substance have been found in almost all vertebrates, even in Petromyzon. They have also been described in the epithelium cells of the mantle in a gasteropod (Purpura lapillus) by Roaf. In Annelids they occur, according to Sommet and Pol, in some of the nerve-cells of the segmental ganglia. This is well seen in the leech, the bloodvessels of which react to adrenine like those of vertebrates. The development of these chromaffine cells is, according to J. F. Gaskell, correlated with that of a muscular vascular system.

Abel has made the remarkable observation that certain patches of skin glands in a large American toad (Bufo aqua) furnish a white, pasty secretion containing a large proportion of adrenine.

Vessels and Nerves.

The bloodvessels are very numerous. The arteries enter at the capsule and give off branches to supply the cortex with a rich capillary network. The bloodvessels do not penetrate the cell-columns of the *zona glomerulora and zona fasiculata* of the cortex, but run in the connective tissue septa between them. In the *zona reticularis* the capillaries are large, have a sinusoid character and come into very close relationship to the cells. They pass into the sinusoids of the medulla. According to Neumann, the bloodsupply of the suprarenal is more abundant than that of any other organ in the body, viz., as much as 6 to 7 c. c. per gramme and per minute with a bloodpressure of 130 m. Hg. This is even higher than that of the thyroid, which comes next with 5 c. c. per gramme and per minute. The respiratory exchange is also very high (Baumann).

In birds and reptiles the suprarenals have a venous bloodsupply as well as an arterial—blood being conveyed to each gland by a "portal" vein which is usually formed by the junction of two or three intercostal veins. The connective tissue septa of the cortex also contain lymphatics, which, like the blood capillaries, pass directly into the vessels of the medulla.

The suprarenals are very richly supplied with nerves. Each suprarenal receives no less than thirty-three nervous filaments (Kölliker) derived partly direct from the splanchnic, partly from the suprarenal plexus, which is itself constituted by branches from the coeliac, phrenic and renal plexuses. After forming a network in the connective tissue capsule, the nerves penetrate into the cortex, partly supplying its bloodvessels, partly its cell-columns. But most of the nerves extend to the medulla, where they form a dense plexus from which filaments pass to end between the secretory cells. Groups of sympathetic nerve-cells are occasionally found both in the medulla and in the deeper parts of the cortex.

Effects of Suprarenal Removal: Epinephrectomy.

Addison's account of the disease he described and which he termed "idiopathic anaemia" led Brown-Séquard (1856) to test the effect of the removal of the suprarenal glands in animals. The operation, which was performed upon a number of animals of different species (rabbits, guinea-pigs, dogs and cats), was followed in every case of double extirpation by a fatal termination within thirty-seven hours of the removal. But a fatal result was produced also in all or nearly all the animals in which the lesion was unilateral, although subsequently Brown-Séquard succeeded in keeping some animals alive for a few days when only one capsule was removed. Since it is now well established that careful removal of one capsule under aseptic precautions is seldom fatal,* there can be little doubt that Brown-Séquard's results were in considerable measure the consequence of, or at any rate were complicated by, shock and sepsis, and that they could not be relied on as a proof that the suprarenal capsules are essential to life. This is indeed the opinion which was formed by most of his contemporaries. Nevertheless, looked at in the light of our present knowledge, it is certain that death must have been either caused or greatly accelerated by the removal of both capsules—since this is now known to be in most animals the invariable result of the double operation and occurs within a few days. There are, however, exceptions, especially in some species of animals: among which the white rat may be particularly mentioned. These exceptions are probably associated with the occurrence of accessory bodies, but whether these must be of cortical or medullary nature—or both—is not determined.

No effect of the extirpation—especially if the operation be performed on the two glands at an interval of a few days—is at first apparent. For some days there is little sign of anything wrong. Then the animal becomes less lively and exhibits signs of muscular weakness. The body temperature also becomes lowered. Soon the weakness becomes extreme, the pulse feeble, the bloodpressure low, and the respiration dyspnoeic. Death soon follows, sometimes immediately preceded by convulsions.

Experiments on adrenal transplantation have for the most part led to negative results. The graft almost invariably undergoes necrosis and disappears, although in some cases the cortical part has seemed to take for a time. Administration of suprarenal extract is unable either in Addi-

*An exception must be made for the guineapig in which unilateral extirpation is frequently followed by death. It may be remarked that the suprarenals are larger in proportion to its size in the guineapig than in any other animal.

son's disease or in the cachexia produced by extirpation, to prevent the usual fatal termination, although this may be somewhat deferred. The muscular weakness characteristic of Addison's disease may for a time tend to disappear with the administration, so that the ergographic record may again approach the normal. But such administration cannot, as in the case of cachexia thyreopriva, take the place of the internal secretion of the gland, and until measures are found to induce an implanted organ to grow, Addison's disease will probably continue to terminate fatally. With the progress of surgery, however, and especially the adoption of the methods of Carrel, the possibility of successful implantation seems less hopeless than was the case only a few years ago.

After extirpation of one gland only there is a compensating hypertrophy of the other, and also of the accessory bodies. Castrated animals were found by Hultgren and Andersson to live much longer after the complete operation than normal individuals. This is also stated to be the case if the complete operation is performed in two stages, first the capsule of the one side and then that of the other being removed. This result is perhaps due to hypertrophy of accessory bodies. With regard to the total amount of suprarenal substance that must remain in order to maintain life, Biedl found that in cats, dogs and rabbits if one-eighth of the whole suprarenal substance is left the animals always survive. He concludes, after a survey of all the experimental evidence on the subject, that it is abundantly proved that "the suprarenals are not only important but are essential to life," and that it is probable that this is due to some material yielded by the cortex—although the loss of the adrenine which is supplied by the medulla may be contributory.

It appears that in other diseases than Addison's the functions of the suprarenal capsules may to a great extent become suppressed. In diphtheria, whether natural or produced experimentally in animals, it has been found that the amount of adrenine yielded by the medulla of the suprarenals is markedly diminished and may even in extreme cases disappear altogether. In cholera also the amount is greatly diminished, and it is stated that in this disease subcutaneous administration of adrenine is markedly beneficial. If the diminution in the amount of adrenine formed should be proved to hold good in other acute infectious disorders, it would seem not improbable that the interference with the functions of the suprarenal capsules is in large measure the cause of the muscular and cardiac weakness and general loss of tone which are prominent symptoms in these affections.

Effects of Administration of Suprarenal Extracts.

If an extract or decoction of suprarenal capsule—made with water or Ringer's solution—is injected into the vein of an animal, the most striking result obtained is an immediate and marked rise of blood-pressure (Oliver and Schäfer, 1894). This can be shown to be caused by contraction of the peripheral arteries. Along with this contraction a slowing of the heart's action may occur due to an effect on the cardio-inhibitory center and may somewhat limit the rise of blood-pressure. But if the vagi are cut, or paralyzed by atropine, the heart beats become enormously accelerated and also augmented in force (primarily by the action of the autacoid on the auricles, but also somewhat on the ventricles*), and this greatly increases the rise of blood-pressure. There is some diminution in the force of the respirations and occasionally a temporary cessation of breathing, especially in the rabbit. But this disappears long before the effect on the bloodvessels has ceased to show itself. The effect upon the vessels lasts a few minutes, gradually passing off: after its passage the blood-pressure is usually a little lower than before. The arteries which are most affected are those of the splanchnic area: those of the limbs and trunk rather less, although the cutaneous vessels are usually strongly contracted: those of the pulmonary system and of the brain only very slightly if at all, and those of the coronary circulation not at all: indeed, in some animals these last are dilated by the extract. According to Barbour, the human coronary arteries are constricted, whilst those of the calf, sheep, pig and other mammals are dilated (inhibited). It is always the smaller vessels which are most affected and in consequence of the great rise of pressure which their contraction produces the larger arteries tend to become passively dilated: this dilatation may be very great. The effect upon the vessels is seen after complete destruction of the central nervous system and after severance of the nerves to the part: indeed, even after the nerves to the vessels have been severed for a long time. It is therefore due to a direct action of the autacoid principle of the gland upon the contractile tissue. Nevertheless, such action only occurs in the case of suprarenal extract in tissues which are supplied with nerves from the sympathetic system, and in the embryo in such tissues only after they have received their nerve supply. And, as has just been stated, severance of the nerves, so far from stopping the action, tends on the contrary to make the tissues supplied by the severed nerve more easily excited by the autacoid**. Gunn and Chavasse have shown that adrenine has also an

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*In birds, as Paton has shown, the augmentation is confined to the auricles.

**This has been found to apply not only to the bloodvessels but also to the pupil (Meltzer and Auer) and to the retractor penis (Fletcher), and is probably of general application.

action upon the muscular coat of veins, causing tonic contraction in the case of peripheral veins and rhythmic contraction in the case of the superior vena cava near the heart.

If the amount of injected extract be great, the rise of blood-pressure caused by vascular contraction and heart acceleration may be enormous—three or four times the normal—and the amount of strain put on the heart is correspondingly great. Sometimes the heart muscle is unable to respond properly under these circumstances and the ventricular action becomes fibrillar—*delirium cordis* being produced, generally leading to instant death. This seems especially liable to occur in a particular phase of early chloroform anæsthesia (Levy). But as a general rule a number of successive injections can be made into a vein and each one will produce an amount of rise of blood-pressure proportionate to the amount of autacoid in the extract: the activity of extracts can in fact be gauged by this method. Other modes of testing the activity of suprarenal extracts are (1) by their action when added to Ringer's solution perfused through the bloodvessels of a frog the central nervous system of which has been destroyed, (2) by the effect produced upon the pupil of the excised eye of a frog when immersed in Ringer's solution to which a definite amount of the extract is added, (3) immersion of the excised uterus of a rat in a similar solution kept aerated by a stream of oxygen, (4) the same, but using a piece of intestine instead of uterus, and (5) the same, but using strips of artery.

The effect of suprarenal extract upon the heart and vessels is not the only action upon plain muscle, although it is the most obvious. Other involuntary muscular tissue supplied by sympathetic fibres is also affected. This may be in the direction of increased contraction (spleen, vagina, uterus*, vas deferens, retractor penis), or of inhibition (intestine, stomach, oesophagus, gall-bladder**). Certain of the plain muscles of the orbit and globe of the eye are also excited so that the eye tends to protrude and the palpebral fissure appears to enlarge: the third eyelid is retracted and the pupil widely dilated (Lewandowsky).***

A flow of saliva similar to that caused by excitation of the cervical sympathetic is also produced and is accompanied by contraction of the vessels of the glands: the flow of saliva is little apparent in the dog, but

*Cushaly has shown that the uterus of a pregnant case is contracted by adrenine whilst the virgin and non-pregnant uterus is usually inhibited.

**In some animals (e. g. ferret) the urinary bladder is contracted by suprarenal extract; in others it is relaxed (Elliott). This again corresponds with the effect of stimulating the sympathetic nerves passing to that viscus.

***Dropping a solution of adrenine into the conjunctival sac does not produce dilatation of the pupil unless the superior cervical ganglia of the sympathetic have been previously removed. This causes the dilatator pupillæ to be more sensitive to the action of the autacoid (see above). It has also been noticed that in diabetes—especially when associated with pancreatic disease or extirpation—the pupil will react to the instilled solution (Löwi).

it is well marked in the cat, in which animal, as is well known, excitation of the sympathetic in the neck provokes an abundant flow from the salivary glands. The lacrimal glands are caused to secrete. Some influence is exerted upon the contraction of skeletal muscle, the curve of which is prolonged, although the latency is not increased. The effect, therefore, is not one of fatigue, but of increased excitability. The autacoid has further been found to defer the onset of fatigue of muscle and to assist its recovery. The arrectores pilorum, especially those of certain parts of the trunk, are stimulated to contract. As a rule there is no increase of sweat secretion. Adrenine also causes contraction of the pigment cells both of the skin and retina of the frog. It is noteworthy that sympathetic stimulation also produces this effect, at least this is so for the pigment cells of the skin. In birds some of the effects are different from those obtained in mammals. Thus in the duck the effect of adrenine is to cause decrease in the strength of the ventricular beats, which may more than compensation for the arterial contraction produced (Noël Paton and Watson). There is also contraction of the intestine instead of inhibition. Although the rule is perhaps not entirely without exception, it may be stated as a general principle that the result of suprarenal injection is identical with that of stimulating the endings of the sympathetic nerves throughout the body (Langley). It has been found by Dixon that if the endings of the sympathetic are paralyzed by apocodein adrenine is without action on the paralyzed parts. Apocodein is known to have the same effect upon the results of sympathetic stimulation.

As has already been pointed out, the above results are obtained even if the sympathetic nerves have been divided and allowed to undergo degeneration. It has, therefore, been concluded that under the influence of these nerves the tissues produce either at the junction of nerve and muscle (myo-neural junction of Elliott) or throughout the cell-protoplasm a material ("receptive or excitable substance" of Langley) which reacts with adrenine, and not only with it but also with other drugs, such as certain alkaloids which have a pronounced physiological action. And further, that this receptive substance increases either in amount or sensitivity after the action of the nerves is withdrawn by their severance.

A very minute dose of the active substance may, as Moore and Purinton showed, produce the reverse action upon the bloodvessels, viz., dilatation instead of contraction. Abolition of the effect of adrenine in producing contraction of plain muscle (and the same applies to the effects of sympathetic excitation) can, as Dale has shown, be obtained by exhibition of ergotoxin—an amine base obtained from ergot and also obtainable from the products of breaking down of histodine. Ergotoxin does not, however, paralyze the inhibition-producing effect of adrenine (or that of sympathetic excitation). Therefore, if, as sometimes hap-

pens, both contraction and inhibition can normally be brought about through the sympathetic and also by adrenine, when the contraction effect is abolished by ergotoxin, the inhibition effect alone appears, and this may produce a reversal of the normal action. Thus after a sufficient dose of ergotoxin, adrenine produces vaso-dilatation in place of vaso-construction, and inhibition of uterine contractions instead of increased contraction. Ergotoxin doubtless acts, like adrenine, on the neuro-muscular junctional or receptive substance.

The action of adrenine upon the terminal apparatus of the sympathetic system is common to a number of primary and secondary amines: the action has been termed "sympatho-mimetic" by Barger and Dale. The more nearly the structure of the amine approaches that of adrenine the more marked is this action. A knowledge of these facts has led to the production of other synthetic drugs having similar properties. The chemical history of adrenine furnishes indeed a striking illustration of the drug-like character of the autacoid substances produced by the endocrine organs.

Repeated intravenous injections into the ear-vein given at intervals of a few days produce (in the rabbit) degenerative sclerosis of arteries (Josué). This action is not specific to the suprarenal autacoid, but is the result of prolonged abnormally high blood-pressure, whether produced by autacoids or by drugs or in any other way.

Local application.—Applied directly to the smaller bloodvessels, the suprarenal autacoid produces marked contraction of the muscular coat (Oliver) and it is therefore of value in surgery as a styptic for arresting haemorrhage from small arteries.

Effects of subcutaneous injection.—Subcutaneous injection of the extract does not produce the rapid effect on involuntary muscle which is so characteristic of intravenous injection—although, as Meltzer and Auer have shown, intramuscular injection may show this result. But large doses of the extract or of the separated autacoid substance of the medulla produce in rabbits and some other animals serious or even fatal symptoms, probably by causing extreme contraction of the arterioles of the central nervous system. After a period of excitement, with rapid pulse and respirations, a period of depression supervenes. Accompanying this depression, the muscular movements are first slowed: there is then paralysis of the limbs and later of the respiratory muscles, with asphyxial convulsions. The body temperature becomes lowered some little while before death. The paralysis is central. *Post mortem* a general hyperaemia of the viscera is evident and abundant haemorrhages are seen to have occurred in various parts. If a first dose is not fatal, a certain amount of immunity may be produced to a subsequent dose (Vincent). The injection also invariably produces glycosuria (Blum), even if the animal has been fed on a diet free from carbohydrates (Noël Paton).

This appears due in part to an action on the liver-cells, in part to an effect on the pancreas: for, as Herter and Wakeman have found, the direct application of the autacoid to the pancreas will cause glycosuria. This will be again referred to in considering the influence of the suprarenal on other glands and in connexion with the internal secretion of the pancreas.

Considerable amounts of the extract can be taken into the stomach without producing any marked physiological result. This is probably due to the fact that the active material is destroyed almost as fast as it is absorbed. That such destruction is readily produced is obvious from the fact that even when large doses are injected into a vein the effects pass off within a few minutes. Where the active substance becomes destroyed is not known, although it has been conjectured that it may be in the tissues generally, especially the muscles and liver. The passing off of the effect may in part also be due to a fatigue of the excited tissues, rendering them less responsive. For it is affirmed that the active principle does not at once disappear from the blood, but may be detected by testing this fluid on another animal. This statement is, however, denied by Trendelenburg. Meltzer finds that adrenine is destroyed by cerebrospinal fluid. (It was shown by Oliver and Schäfer not to be destroyed by blood nor eliminated by the urine.) It has been found by W. Cramer that the autacoid is rapidly inactivated *in vitro* by dilute formaldehyde, and it may well be that the inactivation *in vivo* is brought about by contact with metabolism products which have a similar action.

Influence of nerves on the secretion of adrenine by the suprarenal capsules.—It was shown by Biedl that the stimulation of the splanchnic nerves is accompanied by an increased bloodflow through the organ. The result is even better marked when these nerves have been cut and allowed to degenerate for two or three days so that only the vaso-dilators are acting. Tscherboksaroff, in confirmation of an observation by Dreyer, found that during excitation of the splanchnic in a dog the blood passing from the suprarenal capsule by its vein produces a greater effect in raising the blood-pressure of another dog than the blood of the suprarenal vein under ordinary circumstances, and concluded that adrenine is passed into the traversing blood under the influence of impulses conveyed by these nerves. He also found a larger amount of adrenine in the suprarenal capsules after the stimulation. But the actual proof of secretion under the influence of nerves is most satisfactorily furnished by the experiment of Asher, who found that after ablation of the stomach and intestines and all the other abdominal organs, stimulation of the splanchnics causes a marked rise of blood-pressure, which fails if the suprarenal

bloodvessels are compressed. Elliott and Tuckett were able to exhaust the suprarenal of its adrenine by stimulation of its nerves and Pende found that section of the splanchnics leads eventually to atrophy of the medulla. According to Ehrmann, the secretion is uninfluenced by atropine or pilocarpine, which affect most of the external secretions.

That the passage of adrenine into the blood is always proceeding in sufficient amount appreciably to raise the tone of the bloodvessels seems somewhat doubtful. Oliver and Schäfer found that, even in the blood of the suprarenal vein, there is not always enough to cause a rise of blood-pressure when a few c. c. are injected into a vein. But it is possible by employing more delicate physiological tests—e. g. the reaction with the enucleated eye of the frog or by passing extracts of the dried and deproteinized blood through the bloodvessels of the frog—to obtain evidence in some animals of its presence not only in the blood of the suprarenal vein, but to a less degree in the blood generally. The amount is, however, normally very small, even in the former: not more than about one part in a million, according to Hoskins, McClure and O'Connor. This indicates that the rate of passage into the blood is usually slow: probably it varies at different times. If a very small percentage be present, the blood-pressure may be lowered instead of raised. We cannot, therefore, assume that the normal tone of the vascular system depends on adrenine in the blood, although that the maintenance of vascular tone is in some animals assisted in this manner is shown by the experiment of compressing the suprarenal vein. Such compression may be followed by a considerable fall of blood-pressure, which quickly recovers, and, indeed, more than recovers, its former height on relieving the compression. Temporarily compressing the abdominal aorta produces somewhat similar results. It is possible that the partially resumed tone of peripheral vessels which comes on after section of their nerves may be due to an increase of adrenine in the blood, perhaps assisted by an increase of the autacoid of the posterior lobe of the pituitary body. We must also take into consideration the circumstance that after section of the nerves to plain muscle this tissue becomes much more sensitive to the influence of adrenine.

Trendelenburg estimated the amount of adrenine in the blood of the suprarenal vein of a cat and found that on the average .003 mg. was passed out of the two organs per minute. From the data thus obtained he reckons that about 5 mg. per kilo body weight is formed in 24 hours. After draining off a large quantity of blood and causing a considerable fall of blood-pressure, the amount of adrenine passed per minute was not increased. G. N. Stewart states that nerve massage of the suprarenals leads to the passage of an increased quantity of adrenine into the blood: when the massage is light a depressor effect is caused, when vigorous

a pressor effect; but, according to Hoskins and McClure, never so large a pressor effect as with "ordinary therapeutic dosage."*

Von Aurep finds that stimulation of the splanchnic produces a double rise of blood-pressure; the first being due to direct stimulation of the vasomotors, the second to the outpouring of adrenine into the blood. This latter phase fails to appear if the suprarenals are extirpated. In the cat Cannon found that dilatation of the pupils and upstanding of the fur which accompany sudden alarm or excitement are associated with an increased outpouring of adrenine into the blood, and he has drawn attention to the fact that many of the phenomena which characterize violent emotional states (both in animals and man) are similar to those which are produced by excess of the suprarenal autacoid in the blood. It would further appear that the glycaemia and glycosuria which result from Bernard's sugar puncture is accompanied by and probably largely due to the passage of an excess of adrenine into the blood, causing increased transformation of the liver glycogen into glucose.

Section of the splanchnics diminishes the amount of adrenine which is passed into the blood: according to Elliott, it is only the reflex secretion which is affected; an automatic solution goes on all the time.

Dale and Laidlaw, and Cannon and Bürger, have shown that it is highly probable that certain alkaloids (e. g. nicotine and pilocarpine) exert their action on involuntary muscle, not directly but by stimulating the suprarenals to increased activity. This has also been shown to be the case for morphia, chloroform and ether by Elliott and to be brought about through the splanchnic nerves.

Relations of the Adrenals to Other Glands and Internal Secretions.

Ott and Scott state that various organ extracts produce an increased secretion of adrenine into the blood, viz., thyroid, parathyroid, pituitary, thymus, pancreas, testicle and ovary. The variety of these would seem to indicate that such effect can hardly be indicative of a specific relationship. On the other hand, the secretion of the adrenals has an influence upon many diverse organs and glands—including the other ductless glands—seeing that the autacoid secreted by the medulla activates sympathetic nerve-endings throughout the body.

*It may here be mentioned that so small an addition to the blood of a dog as .005 mg. to 1 liter of blood (equal 1 part in 20 millions) is sufficient to produce a distinct rise of pressure. The same strength of solution of adrenine is sufficient to dilate the pupil of the excised eye of the frog.

With the sexual glands.—A direct relationship between the development of the sexual glands and that of the suprarenals may be regarded as well established, although the nature of the relationship—whether through the nervous system or, as is more probable, through chemical agencies—is not precisely known. The connexion appears to be more with the cortex of the adrenals than with the medulla. During pregnancy the whole gland undergoes enlargement: this change affects the cortex much more than the medulla. Whilst hypertrophy of the cortex is stated to occur as the result of castration, various observers have found that it is also associated with sexual precocity. Further, in diseased conditions resulting in hypoplasia of the adrenals, changes in the testicles, especially in their interstitial cells, have been noted. On the other hand, Elliott and Tuckett deny connexion between the suprarenals and the sexual glands. They associate the cortex more particularly with the development of the muscular system: they also point out that the lower the animal in the vertebrate or at any rate in the mammalian series the greater is the relative development of the cortex. More than one observer has drawn attention to the similarity of appearance between the cells of the cortex of the suprarenals and those of the corpus luteum, but there is at present no evidence of either morphological or functional relationship between these organs.

With other glands.—Injection of suprarenal extract was found by Langley (in the cat) to produce an active secretion of all the salivary and mucous glands of the mouth, gullet and trachea. The secretion is not arrested by small doses of atropine and is similar to that produced by sympathetic excitation. The lacrimal glands are also stimulated to active secretion: and this is said by Yakawa to be the case with the gastric glands as well.

With the liver.—The secretion of bile is increased by adrenine. But the most noteworthy effect on this organ is upon its glycogenic function, for the autacoid of suprarenal medulla even in small doses produces a rapid conversion of the liver glycogen into sugar, which passes into the blood and eventually into the urine. The effect is similar to that caused by Bernard's sugar puncture of the medulla oblongata and by excitation of the splanchnics. On the other hand, after section of the splanchnics Bernard found that puncture of the medulla oblongata fails to cause glycosuria. These effects on the liver are probably in large measure if not entirely due to excitation of the sympathetic fibres passing to the suprarenals, causing the outpouring of an excess of adrenine into the blood and this again excites the

terminal apparatus of the sympathetic nerves in the liver-cells. Kahn noticed that if one adrenal be left its medulla shows indications of over-activity and far less adrenine is stored within it than normally. He states that in the guineapig the blood can be shown to contain an excess of adrenine after the sugar puncture. In confirmation of this A. Mayer found that Bernard's puncture is not effective after removal of the adrenals. Macleod and Pearse have observed that adrenine produces hyper-glycæmia even after division of the hepatic plexus, and that only when the adrenals are intact is it possible to produce hyper-glycæmia by stimulation of the nerves of the liver. Adrenine is therefore in some way necessary to the activity of these nerves: possibly by rendering them more sensitive. Doyen and Gautier state that the effect of adrenine on the liver glycogen can be prevented by atropine. Ergotoxine is also said to antagonize this action of adrenine.

If the liver is free from glycogen, adrenine injection will not only produce glycaemia and glycosuria but may, even in fasting animals, cause glycogen to be stored in considerable quantity: this is associated with the fact that the metabolism of proteins is increased under the influence of adrenine, and the protein is in this case the source of the carbohydrate which is formed (Noël Paton). On the other hand, O. Schwarz has found the liver glycogen to disappear in rats in which the suprarenals have been removed, although it can be restored by liberal feeding with glucose and cane sugar (but not by laevulose or starch). Ringer states that if the glycogen of the liver is got rid of by phlorizin adrenine does not increase the glycosuria.

With the pancreas.—Pemberton and Sweet state that removal of the suprarenals causes a flow of pancreatic juice which is stopped by injection of adrenine, although under normal conditions the flow of pancreatic juice seems not to be affected by the intravenous injection of adrenine in moderate doses. The internal secretion of this organ is however directly affected by this hormone. Herter and Wakeman found that the mere swabbing of the exposed pancreas with adrenine solution provokes an intense glycosuria, comparable with that produced by extirpation of the organ. But the glycosuria and the hyper-glycæmia caused by pancreatic extirpation is increased, as several observers have found, by adrenine, so that the whole of its effect on carbohydrate metabolism is not exerted through the pancreas but part must be directly on the liver-cells. We have in fact already seen that adrenine has a direct effect on the glycogen storage of the liver. But this is influenced by the internal secretion of the pancreas. Thus Zuelzer failed to get adrenine-glycosuria when he injected pancreas extract at the same time as the

adrenine; on the other hand, he states that tying the suprarenal veins is effectual in preventing glycosuria pancreatopriva. These experiments show that carbohydrate metabolism is in some way regulated by the interaction of the adrenals and pancreas upon the liver-cells. Graham Lusk, however, from a study of the respiratory quotient in a glucose-fed dog to which adrenine was administered, comes to the conclusion that this autacoid does not act on carbohydrate metabolism by specifically inhibiting the internal secretion of the pancreas but that its effect on carbohydrate metabolism is related to its vasoconstrictor action. The subject will again come up for discussion when the internal secretion of the pancreas is dealt with.

With the thyroid pituitary body.—The mutual relations of the thyroid and suprarenals have already been discussed under the former organ. Those of the pituitary suprarenals will be considered when the functions of the pituitary are dealt with.

LECTURE IV.

The Pituitary Body, or Hypophysis Cerebri.

The next of the ductless glands to claim our attention is the pituitary body. The study of this organ has sprung into prominence within quite recent years. Although somewhat vaguely connected with growth phenomena and shown (1887) to be related to certain forms of abnormal development of the body and especially of the skeleton, it was not until 1895 that it was suspected of having an active function: by most it was regarded as a rudimentary structure having some morphological interest but little or no physiological importance. Now, on the contrary, it is known that from one portion of the gland important autacoid principles can be extracted which exert an active influence upon some of the most essential organs of the body; whilst from another portion it seems probable that other principles are furnished to the blood which serve as influential chemical regulators of nutrition and growth. Moreover, by most of those who have worked at its functions it is thought to be essential to life. In conformity with this it is found throughout the whole series of Vertebrata with very few exceptions, and these may ultimately prove only apparent.

The pituitary body structure is in man a small organ about the size of a hazel-nut without the shell: it weighs a little more than half a gramme and lies at the base of the brain in the sella turcica of the spheroid bone. It is connected with the floor of the 3rd ventricle by a short, hollow, funnel-shaped stalk—the *infundibulum*. This stalk is composed of nervous tissue, and expands in the interior of the gland into what is known as the nervous part—*pars nervosa*—which when examined by appropriate methods is found to be mainly composed of neuroglia fibres and cells (Herring). In some animals the cavity of the infundibulum with its lining of ependyma is prolonged in the form of a blind canal far into the pars nervosa, but in man this canal has become obliterated, although it existed in the early embryo.

In front of and partly surrounding the pars nervosa the organ is formed of a mass of epithelium cells, granular in appearance and highly vascular. This constitutes the *pars anterior seu glandularis*. In the middle of the organ it is separated from the pars nervosa by a cleft lined by cubical or flattened epithelial cells and filled with glairy fluid. In the adult human subject the cleft is generally found to be obliterated or broken up into isolated cysts containing a colloid-like material. The cleft is all that remains of the original tubular structure of the pars glandularis, which in the early embryo was formed by a

pouch-like outgrowth of the buccal ectoderm (Rathke's pouch) communicating at first with the cavity of the mouth, although ultimately the communication has become obliterated.*

The pars nervosa does not actually abut against the intraglandular cleft, but is separated from it by a layer of epithelial tissue of varying thickness, which was also originally derived from the epithelium of Rathke's pouch but which differs in certain respects from the *pars anterior seu glandularis*—its cells being less granular and its bloodvessels less numerous. This portion of the epithelium is known as the *pars intermedia* since it lies between the *pars anterior* and the *pars nervosa.* From the former it is separated by the cleft just described: from the *pars nervosa* there is no well defined line of separation—indeed cells of the *pars intermedia* may extend for some distance into the *pars nervosa* between its neuroglial fibres, and impart to it an important functional significance, which will be referred to later in considering the mode of secretion of the *pars intermedia.* It is not difficult to split the gland across the middle in the situation of the intraglandular cleft, thus separating the larger *pars anterior* from the combined *pars nervosa* and *pars intermedia.* When such a separation is effected the term *pars posterior* or *posterior lobe* has been given to *pars nervosa+pars intermedia,* the *pars anterior* being termed in contradistinction *anterior lobe.*

Pars anterior seu glandularis.—As already mentioned, this is formed of trabecular masses of epithelium-like cells between which are very numerous sinus-like blood capillaries lying in intimate relation to the cells, which are indeed sometimes set closely round the blood spaces. So abundant are the bloodvessels that a photograph of a section of this part of the injected organ appears almost black: the contrast with the *pars intermedia* and *pars nervosa* being well marked. The *pars anterior* is supplied with blood by about eighteen to twenty small arterioles which converge towards the infundibulum from the circle of Willis and pass into it along the stalk (Dandy and Goetsch). They open into the sinusoidal channels which in this part take the place of capillaries; the blood from these passes away by venules along the stalk. This part of the pituitary probably constitutes the most vascular organ in the body, even more so than the suprarenals.

*Traces of the original connexion with the buccal ectoderm may, however, persist in exceptional cases even in the adult (Erdheim, Haberfeld), as the so-called *pharyngeal hypophysis.* Another vestigial structure—the *parahypophysis*—has been described by Dandy and Goetsch as occurring in the dura mater lining of the sella turcica.

The cells of the *pars anterior* are commonly classified under two main heads, viz., clear, non-staining or chromaphobe, and dark granular. staining or chromaphil: but the granular cells are again divisible into oxyphil and basophil, i. e., those staining with acid and basic dyes respectively, the basophil cells being normally however far the fewer in number. It has been suggested that these three types of cells represent different stages of the same cell, but this is not certain. It is more probably true for the chromaphobe cells and for the cells with oxyphil granules: those with basophil granules appear to be of a different nature. The cells containing oxyphil granules are very distinct. They may sometimes be seen accumulated around the blood-sinuses like the cells of an ordinary secreting gland around the lumen of the alveolus. In some animals all the cells of the *pars anterior* are set like a columnar epithelium round the blood-sinuses—this is strikingly shown in Elasmobranch fishes such as the skate—while in the tortoise columnar cells surround closed vesicles containing a colloid material. The basophil cells are, when present, mostly found near the periphery of the trabecular masses. In pregnancy peculiar large finely-granular cells are observed in considerable number (Erdheim and Stumm): these large cells have been designated "pregnancy cells"; they appear to be merely developments of the chromaphobe cells. Oxyphil cells are described as being unusually abundant in the enlarged gland of acromegalic subjects, where they form adenoma-like masses (Erdheim). All the cells contain numerous fine fatty globules.

Besides the blood-sinuses there is a small amount of reticular connective tissue between the cells. A few nerves have been traced into the *pars anterior* from the *pars nervosa.*

Under certain circumstances in man or mammals, and especially in cases of thyroid absence or insufficiency a product of secretion of the anterior lobe cells which has the appearance of "colloid" appears to accumulate between them, and in parts the cells come to be arranged round the colloid in the form of vesicles which are not very unlike those of the thyroid gland. Normally this appearance is not observed in the *pars anterior* (Herring) although it is characteristically seen in the *pars intermedia.*

Pars intermedia.—As has been stated, the *pars intermedia* although well provided with bloodvessels is far less vascular than the *pars anterior.* At the circumference of the intraglandular cleft these two parts are continuous into one another without a sharp line of demarcation, although it is easily possible to distinguish them by the character of their cells. Behind the intraglandular cleft the *pars intermedia*

forms a well marked layer of varying depth; it also extends as a thin layer over the surface of the *pars nervosa,* as well as over the neck of the gland, connecting the *pars nervosa* with the infundibulum. The cells of the *pars intermedia* have not the coarse oxyphil granules which are characteristic of the granular cells of the *pars anterior,* but they are finely granular. The granules are neutrophil and stain neither with oxyphil nor with basophil dyes. They often surround well defined vesicles occupied by an oxyphil colloid material: occasionally these vesicles are unusually large and numerous, especially in the neighborhood of the intraglandular cleft. In addition to these colloid masses some of the cells of the *pars intermedia* may often be seen in different stages of conversion into globular hyaline bodies, their protoplasm and nucleus becoming swollen; the latter may become indistinct and disappear altogether. Sometimes the globules thus produced may be described as granular in character rather than hyaline. In both cases the cells may break down, setting free the hyaline or granular substance. As has already been mentioned, the *pars intermedia* is by no means everywhere sharply marked off from the pars nervosa, for strands of the cells of the *pars intermedia* may extend a variable distance between the fibres of the *pars nervosa.* The hyaline and granular globules which have been derived from its cells also pass into the substance of the *pars nervosa* and are seen between its fibres: they can in fact be traced as far as the continuation of the third ventricle into the stalk. This fact was first pointed out by Herring, who concluded that it is to be taken as an indication that the hyaline and granular substances which are produced by conversion and breaking down of the cells of the *pars intermedia* form the secretion of this portion of the pituitary and that this secretion thus passes into the cerebro-spinal fluid. In confirmation of this conclusion evidence that the active principle of the posterior lobe of the pituitary is present in cerebro-spinal fluid has been obtained by Cushing and Goetsch, although their conclusion has been traversed by Carlson. The hyaline globules are greatly increased as the result of thyroidectomy (Herring) and also after section of the infundibular stalk (Cushing and Goetsch).

Pars nervosa (also known as the *neuro-hypophysis* or *infundibular body*).—This is formed almost entirely of neuroglia fibres with neuroglia cells scattered amongst them. Many of the fibres arise from these cells, others from the ependyma cells of the infundibulum and of its extension into the gland. Between the neuroglia fibres, especially in the neighbourhood of the stalk but also in other situations, is to be seen the hyaline and granular matter already referred to; sometimes in the

form of swollen cells such as have been described in connexion with the *pars intermedia,* sometimes as amorphous masses; these masses are traceable, as already mentioned, to the infundibulum where they may be seen passing through the ependyma into the cavity of the ventricle. There can be little doubt that the physiological activity of extracts of the *pars nervosa* is connected with the presence of this substance within it, since extracts of ordinary nervous and neuroglial substance have not the same action. Some authors have described nerve-cells within the *pars nervosa*—but according to Herring these do not occur, and there are very few nerve fibres. The *pars nervosa* is the least vascular portion of the pituitary, its bloodvessels being comparatively few in number.

Physiology of the Pituitary—Effects of Extracts.

The discovery in 1895 by Oliver and Schäfer that extracts of pituitary have a remarkable influence upon the vascular system, producing a great rise of blood-pressure with contraction of vessels, led to the attention of physiologists being drawn to this gland, which had up to that time been almost entirely neglected by them. Howell showed that the action is confined to extracts of the posterior lobe—which, as we now know, includes *pars intermedia* and *pars nervosa*—and it has since been shown that it is yielded by extracts of either *pars intermedia* or *pars nervosa* alone, but rather more distinctly by the *pars nervosa* than by the *pars intermedia* (Herring). This is an additional reason for believing that the material which produces this action is formed by the *pars intermedia* and passes from this into and through the *pars nervosa.* The effect of the extract upon the bloodvessels is a direct one and is not due, as is the case of the suprarenal autacoid, to its stimulant action on the sympathetic endings. The effect on the heart is also different; for whereas—with the vagi cut or paralysed—adrenine causes a marked acceleration of the heart (sympathetic stimulation), the pituitary autacoid causes a slowing of the heart's action along with increase in force of the individual beats (Howell).* Moreover, while adrenine either produces no action on the coronary vessels or according to some authors dilates them, the autacoid of the pituitary constricts them as it does other systemic arterioles; and the same is the case with the pulmonary vessels. The pressor or stimulating autacoid also has the peculiarity that, as was first shown by Howell, the effect of a

*In the bird it augments the ventricular contractions, whereas adrenine affects the auricles only in these animals (Paton and Watson).

second dose administered a short interval (30 minutes or less) after the first usually causes no effect; or, if any, not a rise but a fall of blood-pressure (Schäfer and Vincent), which may or may not be followed by a slight rise. Probably therefore there is present in the extract a second autacoid which is antagonistic to the first in its action and should most likely be classed with the chalones or inhibitory autacoids. On the heart's action the repeat dose has the same effect as the first dose, i. e., the beat is strengthened (Biedl). The effect on the uterus (see below) can also be repeated if the autacoid is administered at short intervals. The pressor effect and the effect on the heart produced by the stimulatory autacoid or autacoids usually lasts a considerable time (a quarter to half an hour or more), varying, however, with the dose; the depressor effect of the inhibitory autacoid has a much shorter period of activity. The renal arteries form an exception to the constrictor effect produced by pituitary extract since they dilate as a consequence of the addition of the extract to the circulating blood: the dilatation is correlated with an increase of secretion of urine. This increased secretion may be in part brought about by the increased flow of blood through the kidney vessels, due to the circumstance that they undergo dilatation, while all the other systemic arteries are contracting; but that it is to a certain extent brought about by a specific effect of one of the pituitary autacoids is probable from the fact that it may occur in the absence of an arterial change.*

The extract of pituitary acts upon other plain muscle tissue besides that of the bloodvessels. Thus it powerfully affects the uterus (Dale), even in the minute doses,** as well as the bladder and intestine (Blair Bell and Hick) : it also produces dilatation of the pupil of the excised eye of the frog (Cramer). In some of these actions it resembles adrenine, but the stimulating autacoid of the pituitary is certainly different both chemically and physiologically from that of the suprarenal. Nor does it specifically stimulate structures innervated by the sympathetic as does adrenine; moreover, neither apocodein nor ergotoxine affect the results obtained with it. Probably it produces a direct effect upon the contractile substance of the cells which it stimulates.

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*The effects on the kidney will be more fully dealt with later on.

**The uterus is also rendered more excitable to influences reaching it through its nerves. According to Dale, pituitary extract acts on plain muscle more by increasing its sensitiveness to normal stimuli than by acting as a direct excitant. Thus when administered in pregnancy before the commencement of parturition it produces no effect: but its action during parturition is well marked.

The extracts of posterior lobe also contain an autacoid which influences the secretion of the mammary gland. If injected either into a vein of a lactating animal or intramuscularly in a nursing woman it causes a determination of secretion towards the nipple, accompanied or preceding by a tingling sensation in the breast: and if in a lactating animal the nipple be cut or if a fine canula be inserted into one of the ducts the milk flows out and the gland becomes emptied.*

Lastly, it is found, as with adrenine, that the autacoids of the posterior lobe of pituitary have an important influence upon carbohydrate storage. When injected either into a vessel or subcutaneously they produce disappearance of glycogen from the liver and they facilitate the production of alimentary glycosuria by lowering the limit of assimilation of sugar (Borchardt). Whether all these effects are produced by one and the same active principle has not as yet been definitely determined, for the autacoids of the pituitary have presented much greater difficulties in the way of isolation than those of the suprarenal medulla, although recently more than one investigator has succeeded in obtaining crystalline substances which reproduce the effects of pituitary extract. Herring has obtained certain differences of effect according as the extracts are prepared from the *pars intermedia* or the *pars nervosa*—suggesting that the autacoids undergo some alteration in passing through the latter. Thus the *pars intermedia* of the ox excites the uterine muscle and also the mammary gland more than the plain muscular tissue of the bloodvessels, and has no specific effect on the kidney—nor do repeat doses show any immunity, or hinder extracts of the *pars nervosa* from producing the usual effects on blood-pressure, kidney, etc., as well as its effects on uterus and milk secretion.

Subcutaneous and intramuscular injections—especially the latter—produce effects similar to those caused by intravenous administration, although less rapidly. On the other hand, buccal administration has little or no effect on the bloodvessels, heart and plain muscle. This is not due to destruction of the active material by the gastric juice, but probably to its slow rate of absorption from the alimentary canal. Addition of the gland substance to the food of growing animals or its administration by subcutaneous injection has been alleged by some observers to check growth and delay ossification, but this statement appears to be either inaccurate or not to be of general application. In white rats certainly the growth is not obviously affected by the addi-

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*These effects will be further alluded to later.

tion of small amounts of pituitary to the ordinary food nor is any obvious effect produced upon nitrogenous metabolism. In animals in which the gland has previously been experimentally removed or injured (see below) Cushing has described amelioration of the symptoms as the result of adding large amounts of the gland substance to the food. Pituitary extracts and derivations from them have been administered—with greater or less effect—in a variety of disorders, including surgical shock, intestinal inertia, uterine inertia, amenorrhoea, vesical inertia, deficiency of milk secretion, haemoptysis, exophthalmic goitre, hay fever, rheumatoid arthritis, rickets and osteomalacia.

Effects of Removal or Destruction—Experimental Apituitarism.

A large number of experiments have been made with the view of determining the nature of the symptoms which follow removal of the pituitary. The results of these have been somewhat conflicting in character—due in some measure to the differences of method employed to arrive at the position of the organ, which is obviously a difficult procedure, deeply as it is placed at the base of the brain. Thus while one set of operators (e. g. Horsley and Handelsmann, and Aschner), have preferred to approach it (in animals) through the buccal cavity and basis cranii, in order to avoid disturbance of the brain, others (e. g. Paulesco, Cushing, Biedl) have not hesitated to attack it through a large aperture in the side of the skull, another similar aperture being made on the opposite side so as to enable the hemispheres to be pushed over in order to obtain a good view of the organ; which can in some animals, such as the dog, be got at without much difficulty by this procedure. The former method has the disadvantages (1) that one is working at the bottom of a deep pit from the walls of which blood is constantly oozing so as to obscure the operation, and (2) that it is impossible to secure asepsis. By the use of the lateral method these disadvantages are for the most part avoided but it has been alleged that the serious results which are described as following removal of the organ by this operation are due to shock and paralysis caused by the unavoidable insult to the brain.

Paulesco was the first to state definitely that complete removal is in every case sooner or later fatal. This result was obtained with animals from all classes of vertebrata. Most of the hypophysectomized mammals died within two or three days. He also obtained a fatal result merely by severing the stalk connecting the pituitary body to the base of the brain. Paulesco's statements were confirmed by Harvey Cushing and his fellow workers, who for the most part restricted their experiments to dogs. They found that adult animals usually

succumb after total deprivation in from two to five days, whilst puppies survive longer (ten to thirty days) ; they ascribe this difference to the greater functional adaptability of accessory glandules which are probably present in the roof of the pharynx in young animals. In all cases of long survival a fragment of the gland, including some of the anterior lobe, was found *post mortem* and they attribute the survival to such a remnant. On the other hand, they obtained no definitely recognisable symptoms by severance of the infundibular stalk, a procedure which, as we have seen, Paulesco alleged to be fatal. Removal of part only of the anterior lobe is not at once fatal but leads to certain definite changes in metabolism, which are considered by Cushing to be due to deficient secretion, a condition to which he has given the name *hypopituitarism*. Similar results to those of Paulesco and Cushing have been obtained by Biedl and recently by Ascoli and Legnani.

The symptoms of complete removal or *apituitarism* (cachexia hypophyseopriva) are described by Cushing as follows: On the day after the operation the animal (dog) usually appears normal with fair appetite and no characteristic signs of loss of secretion. Gradually it becomes lethargic, refuses food and responds slowly or not at all to the voice. Later the respiration becomes slow and the pulse both slow and feeble, the musculature limp, often with tremors and fibrillar twitching; the back is arched, and the temperature subnormal; finally, often within 48 hours, the animal becomes comatose and dies in this condition. According to Cushing immediate replantation of the removed gland in some other structure causes an abatement of the symptoms and prolongs life, but whether indefinitely or not is uncertain and would doubtless depend upon whether the graft underwent subsequent degeneration. In Cushing's later experiments extirpation of the gland seems to have been less certainly fatal or longer delayed, the animals exhibiting the symptoms rather of *hypo-* than of *a-pituitarism.* This may be due to small portions of the gland having been left behind or to the employment of younger animals or to the vicarious activity of some other organ or organs. The fact is interesting because Aschner, who has performed a large number of extirpations mainly by the inferior operation (through the base of the skull), has not found the gland to be essential to life—or at least has obtained very considerable prolongation of life after its entire removal. It must, however, be regarded as doubtful if it is possible to effect complete removal by this operation. Aschner himself, who admits the difficulty, regards the small residue as unimportant. In all his cases symptoms of hypopituitarism showed themselves. His animals, if young, remained small: their

milk teeth were retained and also their lanugo hair: their epiphyses did not ankylose. The thyroid was enlarged, the thymus persistent, and the cortex of the suprarenal thickened. In the adult the chief effect of the removal was the putting on of fat. In pregnant animals Aschner found removal of the pituitary to be always followed by abortion.

The experiments of others have yielded different results. Thus Horsley and Handelsmann, who performed complete extirpation in a number of animals chiefly by the operation through the base of the skull, state that although a large proportion of their cases died within forty-eight hours they consider this was due to causes incidental to the operation (shock, haemorrhage, infection). Those that survived showed none of the symptoms above described as characteristic of apituitarism. But in view of the results of clinical observations on the effects of destructive disease of the pituitary it must be regarded as doubtful whether the removal of the gland has been as complete in these cases as in those described by Paulesco and Cushing, the operative method employed by whom seems on the whole less open to objection than that in which the gland is reached through the basi-spheroid.

Experimental hypopituitarism.—The results of lesions which involve only partial removal or destruction are in some respects even more interesting than those in which the extirpation is complete and the symptoms more acute. The most striking effects are obtained in young, growing animals. Retardation of growth after hypophysectomy has been described by various authors and that this is a characteristic of diminished amount of pituitary substance and concomitant diminished secretion of autacoids by the gland has been established by the experiments of Cushing and of Biedl. The work of Aschner, which has just been alluded to, also obviously has an important bearing upon this point, although Aschner himself believes that in most of his operations the removal was complete and that the condition was one of apituitarism. The retardation in development shows itself in a general diminution in size, in imperfection in the ossification process, and in the sexual organs, which long retain their infantile condition. At the same time there is a marked tendency to fat formation, so that the actual weight of the operated animals may exceed that of the controls. Even in adult animals a tendency to obesity is a characteristic feature after partial hypophysectomy. Accompanying this tendency and possibly acting as a causative agent, is a high tolerance for sugars, the limit of alimentary glycosuria being markedly increased. This is the directly contrary effect to that produced by injection of posterior lobe extract and is doubtless the result of deficiency of posterior lobe secretion which in Cushing's opinion "is essential to effective carbo-

hydrate metabolism." It was found by Cushing (in conjunction with Goetsch and Jacobson) that immediately after the operation of partial hypophysectomy a temporary glycosuria would at first usually ensue. This result is perhaps due to a dislodgement of accumulated secretion and irritation due to the injury. The effect, however, soon passes off and is followed by the permanent condition of increased tolerance for sugar. Animals which have acquired this tolerance will suffer loss of the pancreas without becoming diabetic. Injury to the posterior lobe or even its manipulation is, probably for the same reason (release of accumulated secretion and possibly temporary irritation due to the injury), often immediately followed by marked glycosuria and also by polyuria (Schäfer), which may persist long after the glycosuria has disappeared or may be present from the first without glycosuria (diabetes insipidus). In one case of such injury to the pituitary in a dog operated upon by Schäfer the amount of urine rose from 40 c. c. per diem to 230 c. c., and during the following 19 days remained at an average of 119 c. c. In another it rose from 110 c. c., the average of 11 normal days, to 182 c. c., the average of the 11 days immediately succeeding the operation. It was, however, much higher than this on the 3d, 4th and 5th days, averaging 266 c. c. Mere exposure of the pituitary was found to have no such effects. A case in man has been recorded by Simmonds in which there was a malignant tumour of the *pars nervosa* extending to the *pars intermedia,* with marked diabetes insipidus (10 to 19 litres of urine per diem). This is probably a case of the cells of such a tumour assuming the functions of the tissues they are invading (see footnote, page 14). It has been found by Cushing that stimulation of the cervical sympathetic or of its superior ganglion causes diuresis; he considers this is brought about by provoking the secretion of the posterior lobe. Stimulation of the superior cervical ganglion produces no effect if the pituitary be first removed. Therefore, it is concluded that secreting nerves pass through this ganglion to the pituitary. Cushing also states that excision of the posterior lobe or separation of the stalk is sometimes followed by prolonged polyuria: this may be caused by irritation of portions of *pars intermedia* which remain. According to Weed, Cushing and Jacobson, puncture of the pituitary gives as definite results regarding glycosuria as Bernard's puncture of the 4th ventricle. In both cases there must be "available" glycogen present, i. e. glycogen resulting from recent ingestion of carbohydrates. Both this and Bernard's puncture are ineffective after section of the cord at the 4th thoracic level. Mental dullness has also been noticed in partially hypophysectomized animals. Most of the above symptoms have been recognized in the human subject in affections involving the pituitary and presumably also result from hypopituitarism.

Effects of Grafting and Feeding with Pituitary.

Experimental hyperpituitarism.—Many attempts have been made to increase the internal secretion of the pituitary—especially of the *pars anterior*—by grafting the organ or portions of the organ from an animal of the same species into various parts of the body—but these have always so far resulted in failure, the graft disappearing, or at any rate undergoing degeneration, in the course of a few days. In white rats, rabbits and guineapigs I have repeatedly implanted the organ as a whole or in small pieces under the skin of the groin, in the peritoneal cavity, in the kidney substance, in the spleen and in the substance of the brain, but always with no result or with only a temporary effect upon the amount of urine secreted, which has obviously been due to the autacoid of the posterior lobe. Only after extirpation of the animal's own gland did Cushing and his fellow workers succeed in occasionally getting a graft to take (for at least a month). A. Exner seems also to have obtained something like a positive result in rats without previous removal of the animal's own gland, for he states that he was able to observe a temporary increase of growth of animals in which he implanted an extra pituitary as compared with controls. Other methods which might be expected to produce hyperpituitarism consist (1) in the addition of pituitary substance to the food, (2) in the subcutaneous injection of extracts at regular intervals during a prolonged period of time. The second method has been stated by some observers to produce a retardation of growth of the skeleton and of the body generally—a result exactly the contrary to what would be expected if—as there seems no reason to doubt—the symptoms of acromegaly, presently to be described, are due to hypertrophy of the gland, especially of the anterior part. A series of experiments by the first method which were carried out by me upon white rats and extended over several months showed no constant effect in facilitating the growth of young animals—although there was no sign of retardation: the material appears, therefore, to be inert when thus administered. This absence of result may be due to chemical changes effected in the active principles of the anterior lobe by the digestive juices, or it may be that the material of the secretion of the cells of the *pars anterior* is inert whilst within the cells, and only becomes active at the moment of discharge into the bloodstream.

Clinical Evidence.

Clinical symptoms due to overgrowth or deficiency of pituitary.—The clinical symptoms due respectively to overgrowth and to deficiency are characteristic. Although these symptoms have long been recognized,

some of them have only comparatively recently been properly interpreted as the result of pituitary dystrophy. This advance in knowledge has mainly been due to the experiments on animals to which allusion has already been made. The literature of the subject is rapidly becoming enormous. Every day a larger number of cases are recognized to be related to some perversion of function of this organ, and affections which were previously obscure are becoming elucidated. A large number of cases in which the pituitary probably plays a causative part have been described by Harvey Cushing in his book, "The Pituitary Body and Its Disorders," 1910, a work which must in future form the starting point for the study of this organ in its clinical aspects.

The course of many cases of disorder of the pituitary body (termed by Cushing *dyspituitarism*) is as follows: Starting with enlargement of the gland, they are heralded by symptoms of excessive function (*hyperpituitarism*). After a variable time—which may be greatly prolonged—degenerative changes in the enlarged organ supervene and there results from this a gradual diminution (*hypopituitarism*), or even eventually an entire loss of function (*apituitarism*). The primary enlargement is usually first recognized by diminution of the visual field, caused by the pressure of the enlarging gland upon the optic chiasma; hence these affections generally come first under the notice of the ophthalmic surgeon. The loss of vision may not be produced by actual destruction of nerve fibres, for it has frequently been noticed that after operation for removal of the tumour or alleviation of the pressure produced by it the patient's vision is speedily restored. Accompanying the visual symptoms or preceding them certain other signs are developed which point to the advent of a peculiar affection which is known as *acromegaly*, and, in one of its forms, as *gigantism*. The affection to which the name* *acromegaly* was given by Marie (1886) had been already described by others and its association with enlargement of the pituitary body had been recognized. But it is to Marie—associated later with Marinesco—that we owe the first complete account of the syndrome in question. The name which he bestowed upon it expresses its most prominent sign, viz: "hypertrophie singulière non-congénitale des extrémités supérieures, inférieures et céphalique"—a marked non-congenital enlargement of the limbs and head. The hands, feet and face are especially hypertrophied and X-ray photographs show a typical mushrooming of the ungual phalanges. But the enlargement is not confined to the bones of the extremities; it affects the whole skeleton, which becomes thickened and hypertrophied. There is usually a corresponding muscular development;

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*'ἄκρον, extremity; μέγας, large.

the subject becoming abnormally strong. The affection does not supervene until adult life is attained, i. e. until the epiphysial cartilages are ossified, so that the long bones do not grow in length and the stature is but little affected, any increase of stature that is produced by increase of the vertebral column being usually more than compensated for by a kyphosis, which supervenes after the disease has made some progress. But if the hyperpituitarism commences whilst the cartilages are still unossified there is a considerable growth in length of the long bones so that the patient attains an unusual height. The affection is then known as *gigantism,* but is of essentially the same nature and origin as acromegaly (Tamburini, Woods-Hutchinson, Lannois and Roy).*

In practically all cases of both acromegaly and gigantism there is enlargement of the pituitary. This increase in bulk often takes the form of a considerable tumour, which can usually be detected during life in skiagrams of the skull, the sella turcica showing a well-marked enlargement. The tumour is usually found to affect mainly or entirely the anterior lobe, and its character is—at least at first—of the nature of a hyperplasia or adenoma (Benda), although in later stages degenerative or malignant changes may establish themselves. The tumour, if large, is, as already mentioned, liable to affect vision and to produce headache and other symptoms of intracranial pressure.

In addition to the skeletal changes others occur. The integument becomes thickened; there is increased activity of the skin glands and a tendency to an abnormal increase in the growth of the hair over the body (*hypertrichosis*). Diminution of sexual activity often supervenes early in the disease, although it may be preceded by the opposite condition. There is often glycosuria** or simple polyuria: when present these conditions are probably associated with hypertrophy of the posterior rather than of the anterior lobe. As the case advances they may be replaced by high degrees of sugar tolerance, due to a subsequent hypoplasia or degeneration of this lobe. It is interesting to note that in pregnancy also—in which the pituitary is found to undergo enlargement—glycosuria not infrequently occurs.

Marie and Marinesco were originally inclined to the view that acromegaly is due to destructive disease of the gland, since in many cases it is found *post mortem* that the tumour is of malignant character

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*There is little question that most instances of gigantism are pathological, and it is well known that "giants" are comparatively short-lived.

**According to André Levi glycosuria occurs in 30-50% of cases of acromegaly.

and that the substance of the gland has been destroyed.** It was this idea which led to the carrying out by various investigators of experiments for the removal or destruction of the organ in animals, in order to produce, if possible, a similar syndrome. But so far from producing increased growth, this operation led to the opposite result, the development of the skeleton and body generally being retarded and restrained. It is now recognized that the tumours of the gland which are associated with acromegaly are in the first instance of a glandular (adenomatous) type; although they may later become of a malignant or of a cystic nature and lead to the destruction of the glandular tissue. It is, therefore, held by most authorities that the characteristic symptoms of acromegaly are originally due to hyperpituitarism, i. e. to increased function (although it may be that there is also some degree of perversion of function). In later stages effects of destruction may undoubtedly become apparent and supersede the symptoms of hypertrophy.* Since no one has yet succeeded in producing the effects of hyperpituitarism experimentally, either by operation or by feeding with the gland, the evidence of their causation by excess of internal secretion is mainly founded on the clinical features of cases of enlargement of the organ.

Other clinical cases appear to be explicable only by supposing that there exists glandular insufficiency (*hypopituitarism*). There is, as we have seen, evidence derived from the results of partial destruction in animals as to the symptoms which may result from deficiency of secretion (p. 7). When similar symptoms occur in man it is therefore natural to conclude that they have the same cause, viz.: pituitary insufficiency; and in some cases it has been possible to obtain evidence (by skiagrams or post mortem examination) of a deficiency in size of the organ.

It must be stated that by no means every case of tumour of the pituitary is accompanied by the symptoms of acromegaly. For the disease may from the first be destructive and at once tend to the opposite condition, viz.: hypopituitarism, with its own characteristic features. This is probably what happens in the syndrome described by Fröhlich (1901) and termed by Bartels *dystrophia adiposogenitalis.* The symptoms of this affection closely simulate those of animals which have undergone partial or complete removal of the gland. One often quoted case

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**Marie appears more recently to have modified his views; inclining on the whole to the belief that it is a perversion and not a suppression of the secretion which leads to the abnormal growth.

*Sometimes the tumour of the gland is from the first malignant, but it is stated that even then many of the cells tend to resemble those of the normal gland (malignant adenoma) and symptoms of acromegaly are still produced.

in which such symptoms made their appearance was described by Madelung in 1904 in a girl of nine years of age whose pituitary was destroyed by a bullet which lodged in the sella turcica.

The symptoms which are believed to be due to pituitary insufficiency, as might be supposed, are the reverse of those ascribed to hyperpituitarism. If the affection commence before adolescence the stature (instead of becoming gigantic as in hyperpituitarism) remains small. This is generally associated with marked adiposity, so that the weight of the body may be large relatively to the height. Sexual development is delayed and may remain largely in abeyance, producing a more or less permanent condition of sexual infantilism. In the female the menses are irregular or absent and in both sexes there is deficient development of secondary sexual characters such as the hair on the face (in the male) and over the pubes in both sexes. Such hair as occurs in this last mentioned situation in the male does not extend to the umbilicus as usual in that sex, but assumes the disposition characteristic of the female, being limited to the mons veneris. On the other hand, the hair of the head is generally abundant. Nor is the character of the trichosis the only sign of feminism in subjects affected by hypopituitarism. They show also a broad pelvis, with a certain amount of *genu valgum,* small extremities with tapering fingers, and occasionally well-marked mammary development. Skiagrams of the long bones generally exhibit persistent epiphysial lines. The skin is smooth and delicate and free from moisture. The nails are small and thin and the crescents at their base are absent.

The tendency to adiposity is attributable by Cushing to deficiency of posterior lobe secretion. This deficiency is associated with unusual tolerance to sugar and an excessive assimilative power for carbohydrates, which become transformed into fat and thus produce adiposity. These cases are, however, sometimes associated with glycosuria, although more often there is polyuria without sugar (diabetes insipidus).

The hypopituitarism may occur along with simple atrophy of the gland, as appears to be the case in the instance of infantilism described by Dr. Byrom Bramwell (Clinical Studies VI, 1908), in which the skiagram shows a small sella turcica. Or it may be caused in other ways, e. g. by the formation of a cyst partially destroying the gland, or as the result of pressure from a neighboring tumour.

A subnormal body-temperature is generally associated with the above symptoms as well as low arterial tension and a slow pulse; there is also usually drowsiness and torpidity.* The excretion of carbon diox-

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*Most of these symptoms are, as pointed out by Cushing, somewhat similar to those exhibited by hibernating animals.

ide was found by Benedict and Homans to be markedly decreased. Sometimes evidences of psychic derangements and occasionally a tendency to epilepsy have been described.

When the hypopituitarism comes on after adolescence certain of the above symptoms will be missed, but the lowered temperature, the tolerance to sugar and the supervention of excessive adiposity are generally present, as well as the dryness of the skin and loss of hair, and a tendency in the male to adopt the feminine type of trichosis, even in cases where the male type has already been established. According to Cushing, "pigmentation of the skin is a conspicuous feature of many of the adult states, and as it is apt to be associated with asthenia or a low blood-pressure it is natural to ascribe it to an associated adrenal insufficiency, though it hardly reaches the degree of bronzing seen in some of the Addisonian examples of adrenal tuberculosis."

As has already been stated, the history of some cases of affections of the pituitary shows symptoms characterizing hypopituitarism following those characteristic of hyperpituitarism, although of course little or no retrogression in the growth of the skeleton and body can generally be expected. Thus the occurrence of hyperplasia and hyperpituitarism during adolescence leading to a general overgrowth of the body and unusual growth of hair, and sometimes accompanied by sexual precocity, may be followed by glandular hypoplasia and diminution of the sexual instinct, with or without impotence, as well as by excessive adiposity, and the assumption by the male of some of the feminine characteristics which have been above described as associated with hypopituitarism. This alteration in the signs of disease complicates the clinical features of many cases; the complications can only be unravelled by a careful study of the history of each case.

In many instances where the affection begins with hyperplasia of the gland and subsequent changes produce destruction or degeneration of the enlarged organ, leading eventually to apituitarism, these changes may occupy years in their development, but the patient ultimately loses strength and gradually wastes. Under such circumstances death results from a state which is probably analogous to the *cachexia hypophyseopriva* described by Paulesco, Cushing and Biedl in the animals operated on by them. It seems likely that this is the usual course of the disease known as acromegaly, of which it is still uncertain regarding some of the symptoms whether they are to be regarded as associated with hyper- or hypopituitarism. That the acromegalic skeletal growth is produced by hypertrophy and oversecretion (or perverted secretion) of the anterior lobe is highly probable, both as the result of partial extirpation in animals and

from the effect of operative removal of pituitary tumours in man. One case in particular is described by Hochenegg (1908) as having shown within a few days of operation for removal remarkable amelioration of the symptoms, with gradual diminution in size of the enlarged extremities, and eventually complete cure. The thyroid gland both in this and in another instance which was also successfully operated upon by the same surgeon became permanently enlarged. In both the tumour was a malignant adenoma. In other cases operated on by Hochenegg, Cushing and others, in some of which an enlarged anterior lobe only was removed, although the results have for the most part been less striking than in the above examples, the retrogression of the disease symptoms resulting from the partial extirpation of the tumour and especially of its anterior lobe was distinct and apparently permanent.

We are therefore doubtless warranted in believing that the enlargement of the skeleton and the other signs which are characteristic of acromegaly are due to hypertrophy of the anterior lobe of the pituitary, whilst hypertrophy of the posterior lobe produces totally different effects on metabolism. Further, the symptoms due to hypopituitarism vary according as the anterior or the posterior lobe of the gland is mainly affected. In the former case the chief effect seems to be upon the stature. When, however, it is the posterior lobe which is affected, a tendency to fat formation and to deficient sexual development are usually manifested, without being necessarily accompanied by diminution in stature; indeed, they may be associated with increased growth of the body, although not especially affecting the skeleton, and a characteristic infantile condition is retained. Rarely these symptoms of deficiency of posterior lobe occur along with acromegalic symptoms, and are then associated with concomitant enlargement of anterior lobe. That the adiposity is related to a deficiency of the posterior lobe is further indicated by the fact, according to Strada, that it is never accompanied by glycosuria or polyuria, symptoms which are almost certainly the result of increase of activity of that lobe.

In connexion with the influence of the anterior part of the organ on growth, cases of dwarfs have been described in which the pituitary has been noticeably small and atrophied; although on the other hand others have been recorded in which the contrary condition has been found. The supposition that in these latter cases the enlargement is not a true glandular growth as in acromegaly, but of an abnormal or destructive character, is attractive. We must, however, be careful not to adopt it too readily simply because it seems to fit in with what is known of the effect of overgrowth of the organ in producing giants and acromegalics.

But in more than one such case of a dwarf with enlargement of pituitary the tumour has been found to be really outside the gland and to exercise compression upon it. It must be remembered also that increased activity of the natural function of an organ may not necessarily accompany increase in volume: this is exemplified in cases of endemic goitre. There is on the whole, therefore, reason to believe that a dwarfish habit of body is associated with diminution either in size or in activity of the anterior lobe of the pituitary. These changes may commence in infancy or even in the foetus.

Assuming that the two parts of the gland have different functions—the anterior furnishing autacoids which govern the growth of the skeleton and body generally, the posterior, autacoids which affect carbohydrate metabolism, fat formation, and the development of the sex glands as well as stimulate involtary muscle, and certain secretions, especially those of the kidneys and mammary gland, it is obvious that as the result of increase or diminution of volume and function of either part the clinical symptoms manifested in affections in which this organ is involved may take very different characters. Thus we may have symptoms resulting from (1) (2) general hyperpituitarism or hypopituitarism involving both anterior and posterior lobes, (3) (4) anterior hyperpituitarism or hypopituitarism involving the anteroir lobe alone, (5) (6) posterior hyper- or hypopituitarism involving the posterior lobe alone, (7) anterior hyperpituitarism combined with posterior hypopituitarism, and (8) anterior hypopituitarism combined with posterior hyperpituitarism. In all of these eight conditions the clinical appearances would be different.

Relations of the Pituitary to Other Glandular Organs.

The relationship of the pituitary to other glands is more extensive than that of any of the other internally secreting organs. Ascoli and Legnani found, in dogs which survived for a sufficient time the operation of removal of pituitary, a diminution in volume of the spleen, with disappearance of the Malphigian corpuscles, precocious retrogression of the thymus, enlargement of the thyroid due to accumulation of colloid within its follicles similar to that seen in endemic goitre, and an increase of lipoids in the cells of the cortex of the suprarenals.

Relative to the adrenals.—That there is some relationship between the autacoids of the pituitary and of the medulla of the suprarenal capsule would appear from the fact that that of the posterior lobe of the pituitary and that of the suprarenal medulla mutually facilitate one another's action, especially upon the bloodvessels. Thus an immediately prior injection of even a small dose of adrenine will increase the effect of a dose of pituitarine and *vice versa*.

There is also some evidence to show that an excess of adrenine may be secreted into the blood as the result of excitation of the suprarenal medulla by extracts of the posterior lobe of the pituitary.

Relation of pituitary to the sexual glands.—The relationship of the pituitary to the sexual glands and secondary sexual characters has been dealt with in considering the symptoms associated with hypo- and hyper-pituitarism, and besides the effect of these conditions on the state of development of the sexual organs, the latter appear to have some reciprocal effect on the pituitary. Thus several observers have found enlargement of the gland and increase in the number of oxyphil cells of the *pars anterior* to occur as the result of castration; although Biedl and Fichera and Zacher describe the enlargement in the rat as being produced by the appearance of large bladder-like cells, which have not oxyphil granules. Livingston, who has recently made experiments on this subject in rabbits, finds that the effect which is produced is greater in females than in males, being practically negligible in the latter. Steinach and Scheidt state that the changes in the pituitary which would result from castration are prevented by implantation of either ovary or testis in the castrated animal and since the generative cells of the implanted organs undergo atrophy they ascribe the result to the interstitial cells. Moreover, it is found that the conditions of menstruation and pregnancy are associated with hypertrophy of the gland. Indeed, as the result of pregnancy it may attain to twice or three times its normal weight.

Changes in the Pituitary as the Result of Thyroidectomy.

Relation to the thyroid.—That after the removal of the thyroid the pituitary body becomes markedly altered and enlarged was first shown by Rogowitsch in 1886. His statements have been abundantly confirmed by other observers.* The hypertrophy affects all parts, but most the *pars anterior,* in which it is not uncommon to observe a development of colloid-containing vesicles not unlike those of the thyroid: the same appearance is seen in cases of myxoedema and others involving pathological changes in the thyroid in the human subject (Boyce and Beadles and others). But the pituitary colloid is not identical with that of the thyroid. It is noteworthy that it does not contain iodine, which is a characteristic component of the thyroidal colloid in all animals. Even many months after thyroid removal Sutherland Simpson and Andrew Hunter were unable to detect the least trace of iodine in the sheep's pituitary. Nor can the pituitary take the place of the thyroid in animals affected with cachexia thyreopriva. There is, therefore, no clear evidence

*A. E. Livingston has found that thyroid feeding prevents the increase in size of the pituitary which would be caused by thyroidectomy. Halpenny and Thompson obtained enlargement and other changes of the pituitary as the result of parathyroidectomy alone.

that these two organs act vicariously: the effect of the injection of their extracts is, moreover, entirely different. But that they have a certain similarity of function in relation to growth and development is shown by the results of their removal in young animals. In both cases growth is slowed or arrested, the development of the body generally and of the sexual organs in particular is checked and that of the higher functions of the nervous system is interfered with. There is also a tendency to adiposity, which is particularly marked in cases of hypophysial deprivation, but is also seen after thyroidectomy and in myxoedema.

Another striking effect of thyroidectomy upon the pituitary is increase of hyaline and granular masses in the *pars intermedia* and their passage in large numbers through the *pars nervosa* into the infundibular extension of the third ventricle (Herring). This denotes an increased activity of the *pars intermedia.* Whether the phenomenon also occurs in cases of myxoedema has not been noted, but it will probably be found to be the case.

Relation of the pituitary to organs concerned with carbohydrate metabolism.—Hypopituitarism, whether the result of disease or of surgical interference, is associated with an increased tolerance for sugar. This function is, as we have seen, connected with the posterior lobe. According to Cushing, animals which have suffered deprivation of this lobe will even bear removal of the pancreas without exhibiting glycosuria. But the result of removing the pancreas in causing glycosuria is produced through the liver, the glycogen of which becomes converted into sugar. And an effect similar to removal of the pancreas is produced by excess of adrenine in the blood or by swabbing the exposed pancreas with adrenine solution.

Cushing states that after removal of the pancreas the amount of hyaline substance of the *pars intermedia* and *pars nervosa* is increased. All this seems to show that there exists a close functional correlation between these four organs—pituitary, suprarenal, pancreas, and liver, and that disturbance of the function of one of them may affect the metabolism of carbohydrates through its influence upon others. And to these we may add the thyroid, since, as has already been noticed, the mechanism of carbohydrate metabolism is also affected, in some manner as yet imperfectly understood, by a condition of hypothyroidism, which, like hypopituitarism, raises the assimilation limit for sugar in the body; and on the other hand, as the experiments of Asher and Flack have shown, the presence of an unusual amount of thyroid secretion in the blood acts as an excitant to the suprarenals so that an increased outpouring of adrenine is caused, and this produces a lowering of the sugar assimilation limit.

It is, however, upon two of the externally secreting glands that the most obvious effect of the autacoid or autacoids derived from the posterior lobe of the pituitary is exhibited. These are the kidney and the mammary gland. The effect on the kidney is a specific one and may be here more fully alluded to.

Effect of pituitary autacoid upon the kidney.—If the blood-pressure of an animal is measured in the usual way by a manometer and at the same time the volume of the kidney and the rate of urine flow are recorded, it is found that on injecting extract of the posterior lobe or an aqueous solution of its autacoids into a vein, whilst the normal rise of blood-pressure is obtained owing to a general constriction of the arterioles of the body, this constriction is not shared—or only for a very brief interval*—by the kidney, but is here replaced by a dilatation which shows itself by expansion of the organ enclosed in an oncometer. Accompanying this expansion, a remarkable increase in the amount of urine is observed; or if, as often happens after such operation in an anaesthized animal, there is no urine being secreted before the administration of the autacoid, the flow speedily begins, and continues at a rapid although a slowly diminished rate, for a prolonged period of time. It might at first be supposed that the increase of urine is simply determined by the great increase of blood-flow through the organ consequent upon the general vaso-constriction and the local vaso-dilatation which pituitary extract produces. But it may be seen that increased rate of flow is still maintained after the blood-pressure has come back to the level at which it stood before the injection. Moreover, the effect of a second and subequent doses of the autacoid administered soon after the main result of the first dose has passed off again produce an increase in the urine flow, although the blood-pressure as the result of these after-doses does not rise, or even falls instead of rising, and although the kidney volume may now be unaffected. This experiment clearly demonstrates that the autacoid may affect not only the bloodvessels of the organ, but also its secreting cells, which it renders more active (or more permeable). The secretion must therefore in these circumstances be induced by a direct chemical excitation of the renal cells by the autacoid, which thus bears the same relation to the kidneys as is borne by the secretine of the duodenum to the pancreas. In this respect also the action of the autacoid of the pituitary is comparable to that of those drugs which act as specific diuretics upon the secreting cells of the kidney, as distinguished from those

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*During this preliminary period the flow of urine may be temporarily diminished or arrested.

which produce diuresis by increasing the water content of the blood or by merely increasing the general blood-pressure. The question arises whether we have to do here with the action of a single autacoid which acts on the one hand as a chalone upon the bloodvessels of the organ producing their dilatation, and on the other as a hormone upon the secreting cells stimulating them to increased activity, or whether two separate autacoids are concerned, one of which affects the bloodvessels and the other the cells of the organ. The latter view was taken by Herring and myself, but has been combated by Dale, who adduces other examples of the action of drugs and extracts in which the same active substance may produce a double result, one part of which may fail to show itself. If Dale's contention is correct we are, so far as the action upon the kidney and its vessels is concerned, dealing with a single autacoid capable of acting either upon both tissues, viz., bloodvessels and secreting cells, or upon one only. When its action is produced upon one only this may then be interpreted to mean that the other is temporarily insensitive to its action: for example, in the case of the action of pituitary autacoid upon the kidney one may sometimes observe that the diuretic action (upon the cells) fails to be produced whilst the vascular effects are pronounced. But even if this were correct for the kidney, it need not commit us to the conclusion that pituitary extract contains only one autacoid. For there is reason to think that a distinct autacoid affects the secretion of milk; and the fall of blood-pressure produced by a second dose of pituitary extract (see p. 58) is probably due to another; and quite possibly the effects upon the uterus to a third. Baya and Peter have also given evidence for the belief that there are two autacoids which act upon the intestinal muscle, one producing inhibition and the other contraction: they state that they are separable by alcohol.

The diuretic action of the pituitary autacoid is not antagonized by atropine. This may be taken to be a sign that it does not act through nerves or nerve-endings, but directly upon the kidney cells;* in this respect it resembles the action of secretine upon the pancreas.

Effect of extract of posterior lobe of pituitary upon the mammary gland.—It was shown by Ott and Scott that in the goat an injection of this extract into a vein greatly increases the quantity of milk which can be drawn from the udder in a given time after the injection, as compared

*It is usually held that the renal secretion is independent of a direct influence of nerves upon the secreting cells—thus differing from ordinary secreting glands, such as the salivary glands. But Asher has recently adduced evidence which appears to indicate that influences passing down the vagus nerve may affect the quantity of urine secreted by the homolateral kidney.

with that which could be obtained in a similar period immediately before. This galactagogue action of pituitary extract was confirmed by experiments upon lactating cats by Mackenzie and myself. The method we employed consisted in canalizing or incising the nipple of one or two of the mammae so as to allow any milk which was secreted to run out. This was conducted to the side and registered by allowing it to fall upon an electrical drop recorder. This *modus operandi* permits the conditions of the experiment to be readily controlled and the results to be accurately registered. It can thus be shown that even a very minute dose of a pituitary autacoid—whether the same as that which affects the bloodvessels and produces increased secretion of urine cannot certainly be said—will cause milk which has accumulated in the gland to be immediately poured out, whilst a somewhat larger dose will produce complete emptying of the alveoli. If the nipple be not canalized or incised, the resistance which is afforded in the passage through its ducts, controlled as they are by the plain muscle tissue which abounds in the nipple, does not permit of this emptying and no actual outpouring of the secretion takes place. If an intramuscular injection of pituitary extract is made in the arm of a nursing woman, a feeling of tingling is felt in the mamma and a sensation of milk flowing towards the nipple is experienced like that which occurs when the child is put to the breast, but there is no actual outpouring of the secretion.

If in the experiment upon the cat the animal be killed immediately after one of its glands (with nipple incised) has been emptied by an intravenous injection of extract of posterior lobe in the manner above described, and if a portion of tissue comprising parts of two adjacent mammae—one emptied of its secretion as the result of the injection, the other with its alveoli still full of milk—be fixed and sections made passing through both full and empty mammae, the contrast in appearance is remarkable. In the one, where the alveoli are distended with secretion, they are large and rounded and the lining cells are flattened against the limiting membrane, whilst in the other from which the secretion has been discharged the alveoli are irregular, shrunk and empty and their cells are folded, and the lining cells stand prominently out from the limiting membrane.

If after a first full dose of pituitary extract has been given a second dose succeed it at a short interval, no further flow of secretion from the exhausted mamma can be produced. The effect of the autacoid, therefore, is not—at any rate immediately—to cause the cells to form and secrete milk, but only to cause the alveoli to empty themselves of the milk which has been previously formed and secreted within them. The sim-

plest manner in which one can conceive this to occur is by contraction of (plain) muscular tissue around the alevoli. In support of this opinion I have lately succeeded in observing in the well of the mammary alveolus in the cat long rod shaped nuclei immediately external to the epithelium. These nuclei exactly resemble those of involuntary muscle-cells and I have no doubt that they belong to a thin muscular layer which, like the muscular tissue of the sweat-glands, is probably situated between the basement membrane and the epithelium of the alveoli.

The action of pituitary extract upon milk secretion differs from its effect upon the secretion of urine in the fact that in the last named case there is an actual stimulation of the renal cells to abstract fluid from the blood, and not a mere contraction of alveoli and outpouring of previously secreted fluid.

Apart from the pouring out of the contents of the alveoli—or rather the tendency of the alveoli to empty themselves towards the nipple—which is excited by the pituitary galactagogue, there is but little tendency to cause an increased production of milk. This at least is the result which was obtained in cows by Gavin. Later observers (Hammond and Sutherland Simpson) have obtained a slight increase in the diurnal yield of both goats and cows and also a slightly increased amount of fat in the milk produced under the influence of the autacoid.

Mackenzie found that in the cat atropine does not arrest the flow of milk obtained as the result of pituitary injection (an observation which has been confirmed for the cow by Houssay). He obtained, however, an inhibitory action from extracts of placenta, which, when injected into a vein just previously to the injection of pituitary extract, prevented the effect of the latter from influencing the mammary gland. It is reasonable to conclude from this that placenta extract must contain a chalonic autacoid which restrains the outpouring of the secretion of the mamma and antagonizes the harmonic action of the pituitary autacoid.

The mamma is much more sensitive to the action of pituitary extract than are other organs (except perhaps the uterus) and an outflow of milk can be obtained with a dose which produces no appreciable effect on the blood-pressure or kidney. This is well illustrated by an experiment by Herring with the skate's pituitary. In this no effect was shown on the blood-pressure or kidney, but there was abundant outflow of milk. Or it may be that the effect is due to a special hormone and that the one which influences blood-pressure and kidney secretion is absent in the skate's pituitary. The blood of non-lactating animals sometimes contains enough of the galactagogue autacoid to provoke the mammary secretion of a lactating animal, although the other effects of pituitary autacoid

are unseen. Thus in one experiment 5 c. c. of the blood-serum of a guineapig was injected into a lactating cat and provoked a marked secretion from a mamma the nipple of which had been incised, although no effect on the blood-pressure was obtained.

Galactagogue autacoids are also contained in extracts of other organs than the pituitary, viz: the corpus luteum of the ovary, the involuting mucous membrane of the uterus after parturition, the lactating mammary gland itself, and to a slight extent from the pineal gland. Their effect on the mamma is exactly like that of the pituitary galactagogue, but the effects on blood-pressure are either nil or are different from that of pituitary extract. It is possible that in all these cases the galactagogue autacoid is the same as that obtainable from the pituitary.

The effect of galactagogue extracts in causing secretion from the gland is accompanied by a change in the electric potential of the organ so that the alveoli tend to become negative to the duct. This change is somewhat similar to that which is produced in the submaxillary gland as the result of exciting the chorda tympani.

From what has been stated regarding the mammary gland, it is obvious that this is an organ which is singularly under the influence of autacoids circulating in the blood. It is, moreover, well known that its secretion is not directly under the influence of nerves. Excitation of its nerves is not found to produce any effect on the secretion—which, moreover, continues normal after all nerves are cut (Eckard) and even from a gland which has been transplanted to a totally different situation (Ribbert). Moreover, the case of the pyophagus twins, Rosa-Josepha Blazék, who are united by a common sacrum, with anus and vulva in common but with two uteri and vaginae, is particularly interesting in connection with this question. For when one of the twins became pregnant the mammary gland in both underwent hypertrophy and eventually secreted milk. The well-known effects of nervous conditions (emotions and the like) upon milk secretion must therefore be produced through the internal secretions of organs such as the pituitary. That emotions may act in this way is shown by the experiments of Cannon (already referred to), who determined an increase of adrenine in the blood of a cat which had been excited by the presence of a strange dog.

LECTURE V.

The Internal Secretions of the Pineal Gland, of the Alimentary Mucous Membrane, of the Pancreas, and of the Sexual Organs.

The internal secretion of the pineal gland.—The *pineal gland* or *epiphysis cerebri (conarium)*, which is present in nearly all vertebrates, is in man a small solid organ less than half the size of the pituitary body. It projects from the roof or dorsal wall of the third ventricle and is connected on either side by a short stalk or peduncle to the habenular commissure. The base of the gland has a small infundibular depression *(pineal recess)* leading from the ventricle just above the entrance of the aqueduct. This recess is the remains of the evagination from the third ventricle, from which the pineal was originally developed. The gland is somewhat larger in the child than in the adult, and in the female than in the male. Its average weight is given as 0.22 grm. in man. It lies back between the anterior pair of corpora quadrigemina, and is closely invested by pia mater, usually becoming detached from the brain when the pia mater is torn away.

Structure.—Sections of the pineal show it to be composed of epithelium-like cells arranged in irregularly disposed trabeculæ with connective tissue between. In some animals plain muscular tissue has been described in the intertrabecular tissue. The bloodvessels are very numerous. There are no true nervous elements, with the exception of a few fibres apparently destined for the bloodvessels, but neuroglia cells are present in the septa and are said to increase in number with age. Embedded in the interstitial tissue and in the covering of the pia mater are small round globules of calcareous matter—*corpora amylacea, brain sand*—which are much more common in man than in other animals and more numerous in the adult than in the child. The cells of the organ are not everywhere uniform in character. Most of them have a large oval nucleus and a variable number of fine oxyphil granules in their protoplasm, but some possess basophil granules. Comparatively large oxyphil granules such as are seen in the anterior part of the pituitary are not found in the pineal, which otherwise is not very dissimilar in general appearance to that portion of the pituitary in structure, although less vascular. Vesicles containing "colloid" are not present, but cysts are not infrequent: these may be due to pathological changes. The gland undergoes retrogressive changes after puberty: these take the form of hypertrophy of the intertrabecular tissue with diminution in the amount of epithelial tissue: nevertheless this last remains present to some extent throughout life.

Ott and Scott found that the result of intravenous injection of extract of pineal is to produce a fall of blood-pressure followed by a prolonged rise with dilatation of kidney volume and diuresis. They obtained some increase of contraction of the uterus. They state that dilatation of the pupil is produced on dropping the extract into the eye of an animal in which the superior arterial ganglion had been extirpated. They further noticed that the extract has a slight galactagogue action. All these effects are similar to those produced by pituitary extract. The galactagogue action described has been since confirmed by Mackenzie, but Dixon and Halliburton obtained no result so far as arterial pressure and kidney secretion is concerned, apart from a slight fall of blood-pressure, which was almost entirely non-specific. My own experiments have yielded negative results in these particulars and those of Jordan and Eyster were also negative.

Extirpation of the pineal is a difficult operation to carry through without provoking severe hæmorrhage, to which the animals operated on have generally succumbed. The most complete series of experiments as yet made are those of Foà on the domestic fowl. In pullets in which the pineal gland was destroyed no difference could be noted on comparison with controls, but in cockerels Foà describes not only a more rapid growth of body but an earlier development of the testicles and of the secondary sexual characters.

The accounts of the results of castration on the pineal have been conflicting. Those of Sarteschi on male animals of several different species proved negative: whereas Biach and Huller describe in cats, both male and female, the production of an atrophied condition of the pineal as the result of the removal of the generative glands. In connexion with this it is interesting to notice that Schüller and other clinical observers have described abnormal growth of the skeleton and sexual precocity, with early development of secondary sexual characters, in young boys, before the seventh year, in whom tumour of the pineal—generally of the nature of a teratoma—has been discovered *post mortem*. In some of the cases in which secondary sexual characters were present the testicles had remained small, but there was an unusually large amount of the interstitial tissue. The symptoms have been ascribed to a diminution of function of the pineal. Another condition which has been frequently noted as accompanying pineal tumours is unusual adiposity, of a somewhat similar nature to that accompanying hypopituitarism, but not as a rule associated with deficient development of the generative organs. It has been suggested that this may be caused by a condition of hyperpinealism. But it must be admitted that both clinical observations on the subject and experimental observations in animals are at present too fragmentary to

enable us to decide with any precision regarding the functions of this organ or the nature and action of its autacoids.

Internal secretions of the mucous membrane of the alimentary canal.—Bayliss and Starling discovered in 1902 that an extract of the duodenal mucous membrane or even of its epithelium alone, if injected into the circulating blood, produces a secretion of pancreatic juice and, to a less marked degree, of bile. In Bayliss and Starling's experiments the active substance or autacoid was obtained by boiling the mucous membrane with dilute hydrochloric acid and afterwards neutralizing and filtering: the autacoid is contained in the filtrate. They observed little or no activity from extracts of membrane which had not been treated with acid, and concluded that the hormone (*secretine*) is present in the cells in an inactive form (*pro-secretine*) and becomes activated (converted into secretine) by the action of the acid. It had been previously found that rinsing the duodenum with dilute mineral acid* would provoke secretion of pancreatic juice. This had been put down to a reflex effect through nerves and nerve-centers, but the experiments of Bayliss and Starling make it clear that the effect is due to the formation and absorption into the blood of an organic chemical agent of a fairly simple constitution—being dialyzable and not destroyed by boiling.

That there is mutual interaction between pancreas and duodenum would appear from the observations of Evans, who found that prosecretine disappears from the duodenum after complete extirpation of pancreas, but not if enough pancreas be left to prevent the occurrence of glycosuria.

In 1906 Edkins announced that a substance of similar nature to secretine but acting upon the glands of the stomach can be extracted from the pyloric mucous membrane by boiling water or dilute hydrochloris acid, or with dextrose, maltose or albumose.** Extracts of the mucous membrane of the fundus do not yield a similar hormone.

Atropine, which in small doses acts through the nerve-endings of secreting organs, does not inhibit the action of these secretines and, as we have seen, neither does it inhibit the action of the galactagogue autacoids. Their activity is, therefore, probably manifested directly upon the cells of the organ they stimulate and not through the nerve terminations.

The internal secretion of the pancreas.—The pancreas contains, besides its alveoli and the ducts which conduct their secretion into the duo-

*According to Babkin and Ishikawa, fatty acids introduced into the duodenum have a similar effect.

**Albumose has been found by Gley also to activate the pro-secretine of the duodenum.

denum, a peculiar epithelial tissue occurring in most animals in the form of small isolated masses interspersed throughout the gland, and known from their discoverer (1869) as the *islets of Langerhans.* Although quite distinct in appearance and in the characters of their cells from the epithelium of the alveoli, the study of their development shows that they originally grew out from the budding ducts and that their cells have therefore an origin in common with those of the alveoli. But they have no open communication with the ducts or alveoli. The number of islets in the pancreas is very variable, and this variability has led to inferences being drawn regarding their appearance and disappearance, which in many cases are probably not justifiable. Thus Bensley found a variation in the guineapig in animals of different ages of from 10 to 189 islets per milligramme of pancreas: in the mature animal the variation was from 10 to 25. The enumerations of Clerk led him to the conclusion that in the normal human pancreas there may be as many as 10 to 20 islets in each milligramme of the gland, which roughly would give about three-quarters of a million to a million and a half for the whole pancreas.

In Teleostean fishes Rennie has shown that there is one very large mass of islet tissue which is encapsuled by connective tissue and practically forms a separate organ. But in other animals the islets are closely encircled by and in contact with the alveolar tissue and sometimes appear to be contined into it. According to Pensa, they have an especially abundant nerve supply. Each islet has a specialized blood-supply in the form of a network of irregular shaped "sinusoidal" capillaries which are both larger and relatively more numerous than the capillaries of the alveoli (Kühne and Lea).

The cells of the islets are generally much less stained by the ordinary dyes used in histology than are those of the alveoli. They are therefore usually described as chromophobe. But they have an especial affinity, as Bensley has shown, for neutral red and janus green, employed as intravital stains. Although they contain granules, these are much finer than the zymogen granules of the alveolar cells. According to Lane, there are two kinds of cells in the islets, distinguishable from one another by the nature of their granules. The cells come into very close relation—indeed, in actual contact—with the walls of the blood capillaries. If the duct of the pancreas be tied, the ordinary alveolar tissue, after a time, disappears, although for a long while after there are the remains of the chief ducts passing through the organ, but most observers are agreed that the islet tissue does not—at least to any great degree—participate in the atrophy of the alveoli, and the statement that its persistence under these circumstances—although denied by some—is generally accepted,

although it must be admitted that in the altered and cirrhosed tissue of the gland it is not easy to recognize the distinctive features of the islet-cells.

Since the discovery in 1889 by v. Mering and Minkowski, that the removal of the pancreas, or even of the greater part of the organ, is immediately followed by hyperglycæmia leading to severe and fatal diabetes, whereas this effect is not obtained from mere ligature of the duct (in spite of the disappearance of all the alveolar tissue and the complete cessation of formation of pancreatic juice), attention has been especially directed to the islet-tissue as the probable source of an internal secretion which serves to regulate carbohydrate metabolism. For, as has just been stated, the cirrhosed and atrophied gland which remains after ligature of the duct contains none of the ordinary secreting epithelium, except perhaps that of a few remaining ducts, but does, in all probability, still contain the islets of Langerhans. Nevertheless this atrophied gland is sufficient to furnish the autacoid which regulates carbohydrate metabolism, which is by it maintained normal for an indefinite time. But if now the atrophied gland is removed, diabetes at once shows itself. Further, if a portion of pancreas—whether thus atrophied or not—be successfully transplanted to another site and the rest of the gland be then removed, diabetes does not occur—although, on removal of the graft, it immediately makes its appearance. The evidence for the action of an internal secretion which is yielded by the gland—and in all probability by the islet-tissue—which serves to maintain carbohydrate metabolism in a normal condition is therefore very complete. In support of this conclusion it has frequently been noted in cases of diabetes in man that the cells of the islets have undergone some kind of degenerative change.

Regarding diabetes resulting from experimental removal of the pancreas, it may be remarked in the first place that if the removal is complete the percentage of sugar in the urine is very large, even during fasting or on carbohydrate free diet. Minkowski found the relation of dextrose to nitrogen in the dog under these circumstances to be 2.8 :1. With protein diet the sugar rises (and falls) with the nitrogen: with fatty foods there is an increase in the quotient: carbohydrates of the food are almost wholly passed out by the urine as dextrose. Laevulose is, however, to a great extent utilized in the body and the glycogen which had disappeared from the liver and muscles may to some extent reappear when this sugar is given with the food.

The glycosuria is accompanied by hyperglycæmia, which is indeed the actual cause of the glycosuria; but according to de Meyer it is augmented by the fact that the permeability of the kidneys to blood-sugar

seems also to be somewhat increased by absence of the pancreas. The hyperglycæmia is produced in the first instance by transformation of the liver glycogen into sugar, which is passed into the blood; while the glycogen of the muscles is also diminished.* The sugar thus produced from the liver glycogen is not utilized in the body, but is for the most part at once got rid of by the kidneys.** Since, therefore, the carbohydrates of the food are not used for nutrition, there is a comparatively greater call upon the proteins and fats both of the food and of the body, so that the animal loses flesh rapidly and death may ultimately result from inanition, unless the end has arrived sooner as the result of the accumulation in the body of abnormal byeproducts of the metabolism of proteins and fats (such as the acetone-bodies) tending to acidosis and the production of diabetic coma.

The results of pancreas-extirpation and pancreas-grafting can, as we have seen, be best explained by supposing that the islet-tissue produces an autacoid substance which passes into the blood and affects carbohydrate metabolism and carbohydrate storage in such a manner that there is no undue accumulation of glucose in the blood. Provisionally it will be convenient for descriptive purposes to refer to this hypothetical autacoid as *insuline.* It must, however, be stated that it has yet to be determined whether the active substance is present as such in the pancreas or whether it exists there as *pro-insuline,* which becomes elsewhere converted into the active autacoid. It is not found that pancreas extracts have the effect of antagonizing the results of pancreas extirpation: in this respect they offer a parallel to the negative results of suprarenal extracts in antagonizing the effects of adrenal deprivation. On the other hand, it has been shown by Hédon and by Forschbach that the blood of a normal dog contains substances which when allowed to circulate through the system of a depancreatized dog prevent the occurrence of glycosuria. It has also been shown by Carlson and Drennan that if a pregnant bitch be deprived of the pancreas she does not suffer from glycosuria as long as her fœtuses remain *in utero.* This experiment proves that the autacoids produced by the fœtal pancreas can pass to the maternal circulation through the placenta; and both experiments afford a clear indication that the influence of the pancreas upon carbohydrate metabolism is due to a chemical agent circulating in the blood. Later experiments of Hédon

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*Ehrlich found the glycogen of the blood-leucocytes to be markedly increased in amount in pancreatic diabetes.

**Kausch, and independently Noël Paton, have shown that removal of the pancreas in birds does not as a rule cause glycosuria, although glycosuria may be present. On administering adrenine, glycosuria is at once produced.

seem to show that the autacoid is inactive whilst within the pancreatic vein, and only becomes activated on passing through the liver.

There are various ways in which the prevention of an undue accumulation and mobilization of glucose and the consequent appearance of hyperglycæmia might be supposed to be effected by an internal secretion of the pancreas islets:

(1) The active agent may itself be a glycolytic ferment (Lépine) and may be the source of the glycolytic ferment which is known to be present in blood. If so, removal or disease of pancreas would tend to produce glycosuria in consequence of the absence of sufficient of this ferment to effect the splitting of glucose, so that the sugar of the body would not be metabolized further and would be passed out as such by the urine. As against this theory it is found that in diabetes the glycolytic power of the blood is not diminished, and although in support of it the fact has been urged that a glycolytic ferment can be got from the pancreas it must be pointed out that this is by no means peculiar to that organ, for a similar enzyme is yielded by most organs and tissues of the body.

(2) It may be of the nature of a kinase, the function of which is to convert a pro-ferment into ferment or perhaps to promote the activity of an already existing ferment which serves to break down the molecule of glucose and prepare it for ultimate oxidation in the muscles, liver, etc. In support of this hypothesis it is stated by O. Cohnheim that a combination of muscle juice with pancreas juice (obtained from the cells by hydraulic pressure) is far more active glycolytically than either of the two employed singly; although, as Levene points out, the disappearance of sugar which is caused cannot be definitely regarded as glycolysis. According to de Meyer, a glycolytic pro-ferment which is activated by insuline is contained in the blood-leucocytes. Anything which tends to prevent the formation of insuline, such as disease of the islet-tissue (and perhaps the entire removal of the pancreas), the action of adrenine would therefore necessarily interfere with the glycolysis and prevent the utilization of glucose by the tissues, so that hyperglycæmia and glycosuria would be produced. According to this theory, the tissues of a depancreatized dog should be unable or less able to utilize glucose for the production of muscular work. Experiments on heart muscle which seemed to support this have been published by Knowlton and Starling. But other experiments by Porges and Salomon (on skeletal muscle) gave a contrary result, and Starling has since come to the conclusion that his results with Knowlton were within the limits of individual variations of the normal heart muscle.

(3) The substance (insuline) produced by the pancreas islets may be a chalonic autacoid which tends to inhibit the formation of glucose from glycogen, and incidentally to promote the storage of glycogen, so that in its absence the glycogen which is present in the liver is rapidly converted into glucose and the sugar absorbed from the alimentary canal or found in the body is not stored by the liver. The result again will be hyperglycæmia and glycosuria. The fact that the conversion of glycogen into glucose occurs rapidly in the excised liver seems to indicate that there is something which under ordinary circumstances acts as an inhibitory agent, and we may well suppose this to be yielded to the blood by the pancreas.

The hypothesis that there exists a chalonic or inhibitory agent in the internal secretion of the pancreas which affects carbohydrate metabolism is probably the correct one; but whether this is of the nature of an autacoid or of an enzyme cannot be definitely stated, although the supposition that it is an autacoid is most in accordance with what is known regarding the effective agents of other internal secretions.

Relation of internal secretion of pancreas to other endocrine agents.—Hyperglycœmia is produced not only by extirpation of the pancreas but also by Bernard's ring or puncture of the medulla oblongata, by stimulation of the splanchnics, and by the introduction of an excess of adrenine into the blood. That the last named acts in part at least by inhibiting the internal secretion of the pancreas is suggested by the result of its local application, but there is no doubt that its main action is on the twin cells or on their sympathetic endsubstance. In fasting animals adrenine causes disappearance of glycogen from the liver and eventually from the muscles. Repeated doses in the rabbit, although producing further glycosuria, may, singular to relate, be accompanied by a storage of glycogen in the liver. Since this condition is accompanied by increase of nitrogen in the urine, it seems certain that the carbohydrate has now been formed from the disintegration of protein. We have further seen that the sugar-puncture of the medulla oblongata is not effective after removal of the suprarenal (nor, according to Cushing, after extirpation of the pituitary) and probably acts through these organs. Removal of the thyroid prevents, whilst removal of the parathyroids facilitates, both pancreatic and bulbar glycœmia and glycosuria. The thyroid autacoid may therefore be regarded as antagonistic to that of the pancreas, whilst the parathyroid assists it.

We have seen that brushing the pancreas with adrenine provokes marked hyperglycæmia and glycosuria and that this is not merely due to absorption of the autacoid into the general circulation is shown by the fact that the excess of sugar is far greater than when other organs are

so treated. It is not, however, only through the pancreas that adrenine-glycosuria is produced, for it has been shown by various observers that there is an increase of sugar in depancreatized animals, and also in cases of diabetes in man (Paton), as the result of adrenine injection. Moreover, the effect of adrenine is produced immediately both in normal and in depancreatized animals, whereas it takes some hours for the effect of depancreatization upon carbohydrate metabolism to show itself. On the other hand, Zuelzer and others have found that adrenine-glycosuria is prevented by pancreas extracts and even by pancreatic juice: the effect is, however, according to de Meyer, not due to an antagonizing autacoid, but to the effect of the extracts upon the permeability of the kidney for sugar. The result of administering pilocarpine, which produces marked secretion from the pancreas by exciting the secreting endings of the vagi, is also to prevent adrenine-glycosuria: possibly it acts by stimulating the nerve-endings to the islet-cells. An increased tolerance to sugar is associated with diminished activity of thyroid, pituitary (posterior lobe) and suprarenal (medulla): a diminished tolerance with the opposite condition of these glands. According to Eppinger, there is mutual inhibition between the activity of the autacoid of the pancreas which affects carbohydrate metabolism and those of the thyroid and suprarenals: whereas the two last named mutually assist one another. According to Falta and Rudinger, thyroid and parathyroid are mutually opposed in their effect upon sympathetic nerve-endings and through these upon carbohydrate metabolism as influenced by the suprarenals and pancreas.

It will be seen from the above that the whole question of the mode of production of pancreatic diabetes is greatly in need of further elucidation. It would appear, however, that, apart from the liver, which is the chief stockhouse for carbohydrates, a number of organs are concerned in governing the metabolism and mobilization of carbohydrates, all being more or less interdependent. Of these organs the pancreas, with its internal secretion, occupies a central position.

The Internal Secretions of the Generative Glands.

1. *In the male sex.*—It was shown by Leydig in 1850 that the intertubular connective tissue of the testicle is characterized by the presence of strands of epithelium-like cells; these have been termed the "cells of Leydig," and, collectively, "the interstitial gland" of the testis. This varies in development in different species of animals, being very well marked in the cat, less so in the dog and mouse, and still less in the rat and rabbit and in man. It is, however, nearly always present to some extent, and Tandler and Grosz have shown that in animals which undergo

seasonal changes in sexual activity the interstitial cells may be even better developed when the seminiferous tubules are inactive than during the time of their activity, their increased development generally immediately preceding that of the seminiferous epithelium. The tissue may also be found well developed in cases where there is atrophy of the contents of the seminiferous tubules, as in cases of cryptorchidism and after ligature of the vas deferens; although if the whole of the spermatic cord be included in the ligature, so that the circulation and nerve supply to the testicle is interfered with, the interstitial cells may share in the general atrophy of the organ which ensues.

These interstitial cells are polygonal in shape with spherical excentric nuclei, a well-marked nucleolus and a double centrosome. The cytoplasm often contains lipoid granules of a yellowish colour, which are blackened by osmic acid; and also other granules of protein nature, which may be either oxyphil or basophil. Frequently, as shown by Reinke, there are crystals within the cells, but the exact nature of these has not been determined.

Effects of castration.—The results of removal of the testes are well known. If the operation is performed in the child the secondary sexual organs—especially the prostate and seminal vesicles—remain in an undeveloped condition, and other male secondary sexual characters, such as the growth of hair on the face and pubes, the enlargement of the larynx, and the development of the male characters of the skeleton are arrested. In such animals as birds and deer, in which the external characteristics of the male sex are well marked, these fail to show themselves, the general features of development approaching those usual to the female sex. As Sellheim, Geddes and others have shown, modifications occur in the growth of the skeleton, the epiphyses long remaining separate; the limb bones are longer and more delicate than usual, and the sutures of the skull slower in ossifying. The mental characteristics also undergo alteration, tending to retain a more infantile type. Most of the ductless glands are affected, the thyroid and pituitary being diminished, the suprarenal cortex and thymus increased in size: the last named organ shows arrest of its normal retrogressive changes. If castration is performed in the mature animal, and therefore after the secondary sexual characteristics have become developed, there may be some retrogression of these, and such accessory generative glands as the prostate tend to undergo atrophic changes. But the effects now are mainly upon metabolism, shown in a tendency to increased formation of fat, although the limit of assimilation of carbohydrates is lowered and alimentary glycosuria is more easily pro-

duced. How far these effects on metabolism are direct or how far indirect, through the ductless glands, it is not possible to say.

In certain animals which undergo seasonal variations in sexual activity the secondary sexual characters which generally accompany these variations are generally also abolished or modified by castration. Thus in stags, after castration, the antlers either remain undeveloped or if developed are shed prematurely and are either not replaced or replaced only by incomplete growths. But structures which are common to both sexes—where, for instance, both possess horns—are not modified by castration. In Arthropoda this correlation between the generative glands and the secondary sexual characters (which in many species are even more marked than in Vertebrata) does not hold good. Experiments upon caterpillars show that removal of the generative glands has no influence on the development of the male sexual characters of the imago; nor do the glands, if transplanted into individuals of the other sex, affect the secondary sexual characters or instincts of the host. This need not be taken to mean that the secondary sexual characters in these animals are not the result of an internal secretion, but may be interpreted by supposing that some organ other than the generative glands furnishes the internal secretion which produces those characters.

In Vertebrata, at any rate, there can be little doubt that the internal secretions of the generative glands are an important if not the chief factor in determining the development of the secondary sexual characters. And that this development is independent of the normal functions of the generative glands is shown by the fact that the ligature of the vas deferens has no effect in preventing it. Moreover, transplanted testes and even portions of the testis have been found capable (in birds) of preventing the results of castration: the comb, wattles, spurs, etc., of the cock being developed in the usual way. Nussbaum's experiments on the effect upon the development of the thumb-pad of grafting pieces of testis from another frog into the dorsal lymph sac of a castrated male frog also point to the existence of an internal secretion of the testicles in these animals.

It seems certain, therefore, that the development of the secondary sexual characters in the male sex is dependent upon an internal secretion of the testicle and it is highly probable that it is yielded by the interstitial epithelium. This is indicated by various facts. In cryptorchids, and also after experimental ligature of the vas deferens, in both of which, as we have seen, the seminiferous epithelium is atrophied but the interstitial tissue is well developed, the secondary sexual characters and sexual desire are normal. Successful implantation of the whole or part of a testicle in a young castrated animal is also followed by development of those characters, although in many cases the seminiferous epithelium of the graft disappears. Bouin and Ancel state that extract of testicle freed from all morphological elements may, when injected, produce a similar result. In support of the theory that the autacoid which affects the development of the secondary sexual organs and characters is

formed by the interstitial cells they have found that if one testicle be removed from a rabbit and the remaining one have its vas ligatured its interstitial tissue becomes hypertrophied. Further, it is known that if the testicles be treated by X-rays the seminiferous epithelium undergoes degeneration, although the interstitial tissue is not, at first at any rate, attacked. Young animals so treated develop normal secondary sexual characters. On the other hand, remarkable cases have been described, in both male and female sex, in which tumours of the testicle and ovary apparently malignant in character occurring in children have been accompanied by a general growth of stature and by premature appearance of secondary sexual characters, such as growth of hair on the face in the male and in the armpits and on the pubes in both sexes, development of breasts and external generative organs: in short, all the signs of puberty; which, on removal of the tumour, have been found to disappear. These seem to be cases of tumour cells taking on the functions of the normal cells from which they have developed (see Lecture II).

2. *In the female sex.*—The ovary contains besides the Graafian follicles with their ova, follicular epithelium and liquor folliculi, a highly vascular stroma formed of a peculiar connective tissue, firm in texture and containing numerous spindle-shaped cells. In some animals it is possible to discover in the stroma groups of cells of a different appearance from that of the ordinary stroma cells. These have been named the "interstitial cells" of the ovary and have been by some thought to be analogous to the interstitial cells of the testicle. But the evidence in favour of this supposition is far from conclusive. There are also formed during the period of sexual activity—i. e. the period when Graafian follicles are undergoing maturation, with eventual extrusion of the contained ova and liquor folliculi and of part of the follicular epithelium—the so-called *corpora lutea.* These are developments of the burst follicles, but their full development only occurs if pregnancy takes place: otherwise the *corpus luteum* after undergoing a certain amount of development becomes the subject of retrogressive changes and presently atrophies and disappears. But in the event of pregnancy occurring important changes take place both in the follicular epithelium which remains in the burst follicle, and in the vascular wall of the follicle (*theca*) which is derived from the ovarian stroma. The follicular epithelium proliferates and the individual cells become greatly enlarged and filled with lipoid granules (which give the yellowish colour from which the name *corpus luteum* is derived), whilst the inner layer of the *theca* also exhibits proliferation of its cells, and these, along with the bloodvessels, grow in amongst the luteal cells derived from the follicular epithelium. Thus the corpus luteum becomes vascularized

and also provided with a framework of connective tissue, which extends towards the scar formed where the follicle originally burst, in the form of a central strand from which in sections columns of luteal cells appear to radiate.

The corpus luteum is well marked throughout pregnancy, although towards the end it becomes less sharply defined from the ovarian stroma; its cells tending to diffuse into this and eventually losing their characteristic features. Similar changes occur—but with far less increase in size—in burst follicles where pregnancy has not supervened. The *corpora lutea* thus produced have been termed *corpora lutea spuria* to distinguish them from the *corpura lutea vera* of pregnancy. But the mode of formation and of disappearance seems to be similar, although occurring sooner. It seems not improbable that it is some of the cells derived from previous corpora lutea that have been described by various observers as interstitial epithelial cells, for the cells so described closely resemble luteal cells, and in some animals groups of cells derived from corpora lutea which have disappeared remain a long time visible within the stroma.

Effects of spaying. The effects resulting from removal of both ovaries (*oöphorectomy; spaying*) are not so marked externally as in the similar operation in the male sex. If performed in young animals, or if the ovaries are congenitally atrophic, it is not infrequently found that characters distinctive to the male are to some extent assumed. In the human subject, as well as in animals, a constant result is that the uterus remains small: the external changes characteristic of puberty either do not occur or are greatly modified: there is no sign of menstruation. A tendency to the male type of trichosis is often also exhibited. When the operation is performed subsequent to puberty the results are less marked—but menstruation ceases and there is sometimes atrophy of the breasts; in animals a diminution in size of the uterus and Fallopian tubes has been substantiated. Metabolism is affected mainly as in males in the direction of a tendency towards adiposity. This, however, may be indirect and through the ductless glands, which are affected much in the same way as in the male sex by removal of the testicles.

Doubtless, as in the male sex, the effects which are produced by the ovaries in determining the female secondary sexual characters are due to an internal secretion. And reasoning from analogy one would be disposed to refer the production of this not to the generative epithelium but to special cells in the ovarian stroma. Some authorities have looked upon the so-called interstitial cells in this light and have supposed that they correspond with those of the testicle both morphologically and physiologically.

They are, however, affected by the X-rays, whilst those of the testicle are not, and, as we have seen, they show, when present, many analogies with the cells of the corpora lutea. The latter at any rate appear not to be concerned with the secondary sexual phenomena, for it has been shown that heat in animals will still occur if the corpura lutea are destroyed, or if none are present in the ovary. Moreover, the changes which follow spaying can be prevented by ovarian grafts and these may contain no corpora lutea. The grafts may also show after a time no Graafian follicles—these having undergone degeneration and disappearance. This is not, however, a necessary consequence of reimplantation, for instances are recorded of pregnancy supervening after reimplantation of ovaries in spayed animals. Such an occurrence has been reported in the case of a woman by Halliday Croom. But even in the absence of Graafian follicles from the implanted ovarian tissue, Marshall and Jolly and McIlroy have shown that the atrophic changes in the uterus which ordinarily follow spaying are prevented. It would seem, therefore, that the cells of the ovarian stroma, not the generative cells, are the source of the autacoids which maintain the nutrition and integrity of the uterus and produce the secondary sexual characters; but it cannot be stated definitely which are the cells of the stroma that give rise to these autacoids. It is possible that the so-called interstitial cells may so act; but, as we have seen, these are not recognizable as distinct structures in all animals.

Steinach has found that implantation of ovaries into young castrated male rats and guineapigs causes the appearance of certain secondary characters which are essentially feminine, including hyperplasia of mammae and secretion of milk. And similarly he obtained secondary male characters in spayed females in which he succeeded in implanting testicles.

Internal secretion of the corpora lutea.—That the corpora lutea have some internally secreting function is highly probable. Their epithelium is distinctively glandular in appearance and their vascularity suggests that whatever is produced within them is passed directly into the blood. Th. Sack found that if corpus luteum be added to the food of white rats it promotes retention of nitrogen, i. e. laying on of flesh, in females but not in males. That corpora lutea are related to the development of the mammary gland during pregnancy appears from the experiments of Ancel and Bouin and of O'Donoghue, who have found that if in the virgin rabbit a Graafian follicle be ruptured (even by mechanical means) so that a corpus luteum develops, the mammæ undergo evolution; whereas if a corpus luteum fails to form there is no such evolution. Hammond and Marshall find that under these circumstances the development of the mammæ may even proceed so far as to produce free secretion of milk.

The development of corpora lutea in non-pregnant animals is also correlated with marked uterine hyperplasia. Further, extracts of corpus luteum have a stimulating effect on the outpouring of the secretion of the mammary gland only second in activity to that caused by extracts of the posterior lobe of the pituitary. But the chief function of its internal secretion seems to be related to the formation of the uterine decidua and the fixation of the embryo. Fraenkel—working upon a hypothesis suggested by Born—found that if in mammals the corpora lutea are destroyed at an early period of pregnancy the embryo does not become adherent to the mucous membrane of the uterus and ceases to develop. L. Loeb has observed that mechanical stimuli are able to produce the formation of decidual membrane if corpora lutea are present in the ovary, but that there is no such formation in their absence. Extracts of corpus luteum are not in this respect able to replace the functions of the removed organs. Loeb has also shown that in the guineapig the extirpation accelerates bursting of the ripe Graafian follicles, i. e. is conducive to ovulation; from this it may be deduced that their presence militates against ovulation.

It is further stated by Ancel and Bouin that if all the corpora lutea are destroyed in a pregnant rabbit the development of the mammary gland is arrested, and it is inferred that their secretion is necessary for such development. It must, however, be stated that it is difficult to destroy all the corpora lutea in a rabbit's ovary without practically destroying all the ovarian tissue, for the corpora lutea of the pregnant rabbit form by far the greater mass of the ovary.

Internal secretion of uterus.—There is some evidence that in certain states the uterus itself may yield an internal secretion. Bouin and Ancel have described an epithelial formation in the muscular coat of the uterus of the rabbit and guineapig during the latter half of pregnancy which they consider to be related to the development of the mammary glands during the final period of gestation and the production of milk. To this formation they have given the name of "*glande myometricale endocrine.*" Mackenzie found that extracts from the involuting uterus of the cat after parturition causes a free flow of milk from the incised nipple of lactating animals. He obtained no such results with extracts made either from the non-pregnant uterus except shortly after parturition, or from the pregnant uterus. He infers therefore that the uterus contains a galactagogue hormone only at this period.

Internal secretion of mammary gland.—A similar or even better marked galactagogue effect was obtained by Mackenzie as the result of

intravenous injection of extract of lactating mammary gland: although no result is obtained from the gland of non-lactating animals.

Adler states that subcutaneous injection of the extract of mammary gland produces enlargement of the suprarenals and increase of adrenine in the blood, sometimes sufficient to cause glycosuria. He also found it to arrest the development of the embryo and even to produce abortion in pregnant animals.

Internal secretion of the placenta.—Various observers have described experiments which seem to show that hypodermic administration of extract of placenta or feeding with placenta produce growth of the mammary gland and an increased secretion of milk. But Mackenzie found that, so far from the latter being the case, injection of placental extract tends to inhibit the effect of galactagogue extracts such as pituitary or corpus luteum. A similar result was obtained with extract of fœtus, which has also been thought to promote mammary development. It would seem more probable, therefore, that both placenta and fœtus produce chalonic autacoids which have an inhibitory effect on milk secretion; and as a commentary on this it may be noted that the secretion of milk by the mammary gland does not begin to appear until the removal of any influence which may be derived from them.